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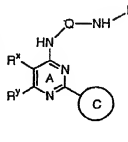
(54) Title: PYRIMIDINE-BASED COMPOUNDS USEFUL AS GSK-3 INHIBITORS



(I)

(57) Abstract: The present invention provides a compound of formula (I): (I), or a pharmaceutically acceptable derivative thereof. These compounds are inhibitors of protein kinases, particularly inhibitors of GSK-3 mammalian protein kinases. The invention also provides pharmaceutically acceptable compositions comprising the compounds of the invention and methods of utilizing those compounds and compositions in the treatment of various protein kinase mediated disorders. such as diabetes, cancer, stroke and Alzheimer's disease.

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PYRIMIDINE-BASED COMPOUNDS USEFUL AS GSK-3 INHIBITORS

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] The present application claims priority under 35 U.S.C. § 119(e) to U.S. Provisional Application number 60/338,857, filed December 7, 2001, entitled "Pyrimidine-Based Compounds Useful as GSK-3 Inhibitors", the entire contents of which are hereby incorporated by reference.

FIELD OF THE INVENTION

[0002] The present invention is in the field of medicinal chemistry and relates to compounds that are protein kinase inhibitors, compositions containing such compounds and methods of use. More particularly, this invention relates to compounds that are inhibitors of Glycogen synthase kinase-3 (GSK-3). The invention also relates to methods of treating diseases associated with the protein kinase GSK-3, such as diabetes, cancer, stroke, and Alzheimer's disease.

BACKGROUND OF THE INVENTION

[0003] The search for new therapeutic agents has been greatly aided in recent years by better understanding of the structure of enzymes and other biomolecules associated with target diseases. One important class of enzymes that has been the subject of extensive study is the protein kinases.

[0004] Protein kinases mediate intracellular signal transduction. They do this by effecting a phosphoryl transfer from a nucleoside triphosphate to a protein acceptor that is involved in a signaling pathway. There are a number of kinases and pathways through which extracellular and other stimuli cause a variety of cellular responses to occur inside the cell. Examples of such stimuli include environmental and chemical stress signals (e.g. osmotic shock, heat shock, ultraviolet radiation, bacterial endotoxin, H_2O_2), cytokines (e.g. interleukin-1 (IL-1) and tumor necrosis factor α (TNF-α)), and growth factors (e.g. granulocyte macrophage-colony-stimulating factor (GM-CSF), and fibroblast growth factor (FGF). An extracellular stimulus may effect one or more cellular responses related to cell growth, migration, differentiation, secretion of hormones, activation of transcription factors,

muscle contraction, glucose metabolism, control of protein synthesis and regulation of cell cycle.

[0005] Many diseases are associated with abnormal cellular responses triggered by protein kinase-mediated events. These diseases include autoimmune diseases, inflammatory diseases, neurological and neurodegenerative diseases, cancer, cardiovascular diseases, allergies and asthma, Alzheimer's disease and hormone-related diseases. Accordingly, there has been a substantial effort in medicinal chemistry to find protein kinase inhibitors that are effective as therapeutic agents.

[0006] Glycogen synthase kinase-3 (GSK-3) is a serine/threonine protein kinase comprised of α and β isoforms that are each encoded by distinct genes [Coghlan et al., *Chemistry & Biology*, **7**, 793-803 (2000); and Kim and Kimmel, *Curr. Opinion Genetics Dev.*, **10**, 508-514 (2000)]. GSK-3 has been implicated in various diseases including diabetes, Alzheimer's disease, CNS disorders such as manic depressive disorder and neurodegenerative diseases, and cardiomyocyte hypertrophy [WO 99/65897; WO 00/38675; and Haq et al., *J. Cell Biol.* (2000) **151**, 117-130]. These diseases may be caused by, or result in, the abnormal operation of certain cell signaling pathways in which GSK-3 plays a role. GSK-3 has been found to phosphorylate and modulate the activity of a number of regulatory proteins. These proteins include glycogen synthase, which is the rate limiting enzyme necessary for glycogen synthesis, the microtubule associated protein Tau, the gene transcription factor β-catenin, the translation initiation factor e1F2B, as well as ATP citrate lyase, axin, heat shock factor-1, c-*Jun*, c-*myc*, c-*myb*, CREB, and CEPBα. These diverse protein targets implicate GSK-3 in many aspects of cellular metabolism, proliferation, differentiation and development.

[0007] In a GSK-3 mediated pathway that is relevant for the treatment of type II diabetes, insulin-induced signaling leads to cellular glucose uptake and glycogen synthesis. Along this pathway, GSK-3 is a negative regulator of the insulin-induced signal. Normally, the presence of insulin causes inhibition of GSK-3 mediated phosphorylation and deactivation of glycogen synthase. The inhibition of GSK-3 leads to increased glycogen synthesis and glucose uptake [Klein et al., *PNAS*, **93**, 8455-8459 (1996); Cross et al., *Biochem. J.*, **303**, 21-26 (1994); Cohen, *Biochem. Soc. Trans.*, **21**, 555-567 (1993); and Massillon et al., *Biochem J.* **299**, 123-128 (1994)]. However, in a diabetic patient, where the insulin response is impaired, glycogen synthesis and glucose uptake fail to increase despite the presence of relatively high blood levels of insulin. This leads to abnormally

high blood levels of glucose with acute and long term effects that may ultimately result in cardiovascular disease, renal failure and blindness. In such patients, the normal insulin-induced inhibition of GSK-3 fails to occur. It has also been reported that in patients with type II diabetes, GSK-3 is overexpressed [WO 00/38675]. Therapeutic inhibitors of GSK-3 are therefore potentially useful for treating diabetic patients suffering from an impaired response to insulin.

[0008] GSK-3 activity has also been associated with Alzheimer's disease. This disease is characterized by the well-known β-amyloid peptide and the formation of intracellular neurofibrillary tangles. The neurofibrillary tangles contain hyperphosphorylated Tau protein, in which Tau is phosphorylated on abnormal sites. GSK-3 has been shown to phosphorylate these abnormal sites in cell and animal models. Furthermore, inhibition of GSK-3 has been shown to prevent hyperphosphorylation of Tau in cells [Lovestone et al., *Current Biology* **4**, 1077-86 (1994); and Brownlees et al., *Neuroreport* **8**, 3251-55 (1997)]. Therefore, it is believed that GSK-3 activity may promote generation of the neurofibrillary tangles and the progression of Alzheimer's disease.

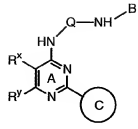
[0009] Another substrate of GSK-3 is β-catenin which is degradated after phosphorylation by GSK-3. Reduced levels of β-catenin have been reported in schizophrenic patients and have also been associated with other diseases related to increase in neuronal cell death [Zhong et al., *Nature*, **395**, 698-702 (1998); Takashima et al., *PNAS*, **90**, 7789-93 (1993); and Pei et al., *J. Neuropathol. Exp*, **56**, 70-78 (1997)].

[0010] GSK-3 activity has also been associated with stroke [Wang et al., *Brain Res*, 859, 381-5 (2000); Sasaki et al., Neurol Res, 23, 588-92 (2001); Hashimoto et al., *J. Biol. Chem,* 277, 32985-32991 (2002)].

[0011] Considering the lack of currently available treatment options for the majority of the conditions associated with GSK-3 and other protein kinases, there is still a great need for new therapeutic agents that inhibit these protein targets.

SUMMARY OF THE INVENTION

[0012] The present invention addresses this need by providing compounds and pharmaceutical compositions thereof that are effective as protein kinase inhibitors, particularly as inhibitors of GSK-3. These compounds have the general formula **I**:



I

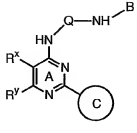
or a pharmaceutically acceptable derivative or prodrug thereof, wherein B, Q, Ring C, R^X, and R^Y are as defined below.

[0013] In another embodiment, the invention provides pharmaceutical compositions comprising a GSK-3 inhibitor of this invention. These compositions may be utilized in methods for treating or preventing a variety of GSK-3 mediated conditions, such as neurodegenerative disorders, diabetes, Alzheimer's disease, Huntington's Disease, Parkinson's Disease, AIDS-associated dementia, amyotrophic lateral sclerosis (ALS, Lou Gehrig's Disease), multiple sclerosis (MS), schizophrenia, cardiomyocyte hypertrophy, reperfusion/ ischemia, baldness, and stroke.

[0014] The compositions of this invention are also useful in methods for enhancing glycogen synthesis and/or lowering blood levels of glucose and therefore are especially useful for diabetic patients. These compositions are also useful in methods for inhibiting the production of hyperphosphorylated Tau protein, which is useful in halting or slowing the progression of Alzheimer's disease. Another embodiment of this invention relates to a method for inhibiting the phosphorylation of β–catenin, which is useful for treating schizophrenia.

DESCRIPTION OF THE INVENTION

[0015] It has now been found that compounds of this invention and pharmaceutical compositions thereof are effective as protein kinase inhibitors, particularly as inhibitors of GSK-3. These compounds have the general formula I:



I

or a pharmaceutically acceptable derivative or prodrug thereof, wherein:

B is an optionally substituted 5-6 membered monocyclic or 8-10 membered bicyclic aromatic ring, wherein said monocyclic or bicyclic ring has 0-4 heteroatoms selected from oxygen, sulfur or nitrogen;

Q is a C_{1-4} alkylidene chain, wherein each methylene unit of said Q is substituted by R^2 and $R^{2'}$, and up to two non-adjacent methylene units of said Q are optionally and independently replaced by $-SO_2$ or -C(=O);

Ring C is selected from a phenyl, thienyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, or 1,2,4-triazinyl ring, wherein said Ring C optionally has one or two ortho substituents independently selected from $-R^1$, any substitutable carbon position on Ring C is independently substituted by $-R^5$, or two adjacent substituents on Ring C are optionally taken together with their intervening atoms to form a fused, unsaturated or partially unsaturated, 5-6 membered ring having 0-3 heteroatoms selected from oxygen, sulfur or nitrogen, said fused ring being optionally substituted by halo, oxo, or $-R^8$;

R^1 is selected from –halo, -CN, $-NO_2$, T-V-R^6, phenyl, 5-6 membered heteroaryl ring, 5-6 membered heterocyclyl ring, or C_{1-6} aliphatic group, said phenyl, heteroaryl, and heterocyclyl rings each optionally substituted by up to three groups independently selected from halo, oxo, or $-R^8$, said C_{1-6} aliphatic group optionally substituted with halo, cyano, nitro, or oxygen, or R^1 and an adjacent substituent taken together with their intervening atoms form said ring fused to Ring C;

each R^2 is independently selected from H, -OH, C_{1-10} aliphatic; (C_{1-10} aliphatic)-NH-(C_{1-10} aliphatic); -O-(C_{1-10} aliphatic); $-NH_2$, $-NH(C_{1-10}$ aliphatic), $-N(C_{1-10}$ aliphatic)$_2$, -C(=O)R, aryl, or heteroaryl, wherein said aliphatic, aryl, or heteroaryl is optionally substituted;

R is selected from an optionally substituted group selected from C_{1-10} aliphatic, aryl, aralkyl, heteroaryl, or heteroaralkyl;

each $R^{2'}$ is independently selected from H or an optionally substituted C_{1-10} aliphatic group;

R^X and R^Y are independently selected from T-R^3, or R^X and R^Y are taken together with their intervening atoms to form a fused, partially saturated or aromatic, 5-8 membered ring having 0-3 ring heteroatoms selected from oxygen, sulfur, or nitrogen, wherein any substitutable carbon on said fused ring formed by R^X and R^Y is substituted by oxo or T-R^3, and any substitutable nitrogen on said ring formed by R^X and R^Y is substituted by R^4;

T is a valence bond or a C_{1-4} alkylidene chain;

R^3 is selected from –R', -halo, -OR', -C(=O)R', -CO_2R', -COCOR', -$COCH_2$COR', -NO_2, -CN, -S(O)R', -$S(O)_2$R', -SR', -$N(R^4)_2$, -CON$(R^7)_2$, -$SO_2N(R^7)_2$, -OC(=O)R', -$N(R^7)$COR', -$N(R^7)CO_2$(optionally substituted C_{1-6} aliphatic), -$N(R^4)N(R^4)_2$, -C=NN$(R^4)_2$, -C=N-OR', -$N(R^7)CON(R^7)_2$, -$N(R^7)SO_2N(R^7)_2$, -$N(R^4)SO_2$R, or -OC(=O)N$(R^7)_2$;

each R' is independently selected from hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, C_{6-10} aryl, a heteroaryl ring having 5-10 ring atoms, or a heterocyclyl ring having 5-10 ring atoms;

each R^4 is independently selected from –R^7, -COR^7, -CO_2(C_{1-6} aliphatic), -CON$(R^7)_2$, or -SO_2R^7, or two R^4 on the same nitrogen are taken together to form a 5-8 membered heterocyclyl or heteroaryl ring;

each R^5 is independently selected from –R', halo, -OR', -C(=O)R', -CO_2R', -COCOR', -NO_2, -CN, -S(O)R', -SO_2R', -SR', -$N(R^4)_2$, -CON$(R^4)_2$, -$SO_2N(R^4)_2$, -OC(=O)R', -$N(R^4)$COR', -$N(R^4)CO_2$(optionally substituted C_{1-6} aliphatic), -$N(R^4)N(R^4)_2$, -C=NN$(R^4)_2$, -C=N-OR', -$N(R^4)CON(R^4)_2$, -$N(R^4)SO_2N(R^4)_2$, -$N(R^4)SO_2$R', or -OC(=O)N$(R^4)_2$, or R^5 and an adjacent substituent taken together with their intervening atoms form said ring fused to Ring C;

V is –O-, -S-, -SO-, -SO_2-, -$N(R^6)SO_2$-, -$SO_2N(R^6)$-, -$N(R^6)$-, -CO-, -CO_2-, -$N(R^6)$CO-, -$N(R^6)$C(O)O-, -$N(R^6)$CON(R^6)-, -$N(R^6)SO_2N(R^6)$-, -$N(R^6)N(R^6)$-, -C(O)N(R^6)-, -OC(O)N(R^6)-, -$C(R^6)_2$O-, -$C(R^6)_2$S-, -$C(R^6)_2$SO-, -$C(R^6)_2SO_2$-, -$C(R^6)_2SO_2N(R^6)$-, -$C(R^6)_2N(R^6)$-, -$C(R^6)_2N(R^6)$C(O)-, -$C(R^6)_2N(R^6)$C(O)O-, -$C(R^6)$=NN(R^6)-, -$C(R^6)$=N-O-, -$C(R^6)_2N(R^6)N(R^6)$-, -$C(R^6)_2N(R^6)SO_2N(R^6)$-, or -$C(R^6)_2N(R^6)$CON(R^6)-;

each R^6 is independently selected from hydrogen or an optionally substituted C_{1-4} aliphatic group, or two R^6 groups on the same nitrogen atom are taken together with the nitrogen atom to form a 5-6 membered heterocyclyl or heteroaryl ring;

each R^7 is independently selected from hydrogen or an optionally substituted C_{1-6} aliphatic group, or two R^7 on the same nitrogen are taken together with the nitrogen to form a 5-8 membered heterocyclyl or heteroaryl ring; and

each R^8 is independently selected from an optionally substituted C_{1-4} aliphatic group, -OR^6, -SR^6, -COR^6, -SO_2R^6, -$N(R^6)_2$, -$N(R^6)N(R^6)_2$, -CN, -NO_2, -CON$(R^6)_2$, or -CO_2R^6.

[0016] As used herein, the following definitions shall apply unless otherwise indicated.

[0017] The phrase "optionally substituted" is used interchangeably with the phrase "substituted or unsubstituted." Unless otherwise indicated, an optionally substituted group may have a substituent at each substitutable position of the group, and each substitution is independent of the other.

[0018] The term "aliphatic" or "aliphatic group", as used herein, means a straight-chain or branched, substituted or unsubstituted C_1-C_8 hydrocarbon chain that is completely saturated or that contains one or more units of unsaturation, or a monocyclic C_3-C_8 hydrocarbon or bicyclic C_8-C_{12} hydrocarbon that is completely saturated or that contains one or more units of unsaturation, but which is not aromatic (also referred to herein as "carbocycle" "cycloaliphatic" or "cycloalkyl"), that has a single point of attachment to the rest of the molecule wherein any individual ring in said bicyclic ring system has 3-7 members. For example, suitable aliphatic groups include, but are not limited to, linear or branched, substituted or unsubstituted alkyl, alkenyl, alkynyl groups and hybrids thereof such as (cycloalkyl)alkyl, (cycloalkenyl)alkyl or (cycloalkyl)alkenyl.

[0019] The terms "alkyl", "alkoxy", "hydroxyalkyl", "alkoxyalkyl", and "alkoxycarbonyl", used alone or as part of a larger moiety include both straight and branched chains containing one to twelve carbon atoms. The terms "alkenyl" and "alkynyl" used alone or as part of a larger moiety shall include both straight and branched chains containing two to twelve carbon atoms.

[0020] The term "heteroatom" means nitrogen, oxygen, or sulfur and includes any oxidized form of nitrogen and sulfur, and the quaternized form of any basic nitrogen. Also the term "nitrogen" includes a substitutable nitrogen of a heterocyclic ring. As an example, in a saturated or partially unsaturated ring having 0-3 heteroatoms selected from oxygen, sulfur or nitrogen, the nitrogen may be N (as in 3,4-dihydro-2*H*-pyrrolyl), NH (as in pyrrolidinyl) or NR^+ (as in N-substituted pyrrolidinyl).

[0021] The term "unsaturated", as used herein, means that a moiety has one or more units of unsaturation, and includes aryl rings.

[0022] The term "aryl" used alone or as part of a larger moiety as in "aralkyl", "aralkoxy", or "aryloxyalkyl", refers to monocyclic, bicyclic and tricyclic ring systems having a total of five to fourteen ring members, wherein at least one ring in the system is aromatic and wherein each ring in the system contains 3 to 7 ring members. The term "aryl" may be used interchangeably with the term "aryl ring". The term "aryl" also refers to heteroaryl ring systems as defined hereinbelow.

[0023] The term "heterocycle", "heterocyclyl", "heterocycloaliphatic", or "heterocyclic" as used herein means non-aromatic, monocyclic, bicyclic or tricyclic ring systems having five to fourteen ring members in which one or more ring members is a heteroatom, wherein each ring in the system contains 3 to 7 ring members.

[0024] The term "heteroaryl", used alone or as part of a larger moiety as in "heteroaralkyl" or "heteroarylalkoxy", refers to monocyclic, bicyclic and tricyclic ring systems having a total of five to fourteen ring members, wherein at least one ring in the system is aromatic, at least one ring in the system contains one or more heteroatoms, and wherein each ring in the system contains 3 to 7 ring members. The term "heteroaryl" may be used interchangeably with the term "heteroaryl ring" or the term "heteroaromatic".

[0025] An aryl (including aralkyl, aralkoxy, aryloxyalkyl and the like) or heteroaryl (including heteroaralkyl and heteroarylalkoxy and the like) group may contain one or more substituents. Suitable substituents on the unsaturated carbon atom of an aryl, heteroaryl, aralkyl, or heteroaralkyl group are selected from halogen, -R°, -OR°, -SR°, 1,2-methylenedioxy, 1,2-ethylenedioxy, phenyl (Ph) optionally substituted with R°, -O(Ph) optionally substituted with R°, $-CH_2$(Ph) optionally substituted with R°, $-CH_2CH_2$(Ph),optionally substituted with R°, $-NO_2$, -CN, $-N(R°)_2$, -NR°C(O)R°, -NR°C(O)N(R°)$_2$, -NR°CO_2R°, -NR°NR°C(O)R°, -NR°NR°C(O)N(R°)$_2$, -NR°NR°CO_2R°, -C(O)C(O)R°, -C(O)CH_2C(O)R°, -CO_2R°, -C(O)R°, -C(O)N(R°)$_2$, -OC(O)N(R°)$_2$, -S(O)$_2$R°, -SO_2N(R°)$_2$, -S(O)R°, -NR°SO_2N(R°)$_2$, -NR°SO_2R°, -C(=S)N(R°)$_2$, -C(=NH)-N(R°)$_2$, or $-(CH_2)_qNHC(O)R°$ wherein q is 0-2, and wherein each R° is independently selected from hydrogen, optionally substituted C_{1-6} aliphatic, an unsubstituted 5-6 membered heteroaryl or heterocyclic ring, phenyl, -O(Ph), or $-CH_2$(Ph), or wherein two occurrences of R°, on the same substituent or different substituents, taken together, form a 5-8-membered heterocyclyl or heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Optional substituents on the aliphatic group of R° are selected from NH_2, NH(C_{1-4} aliphatic), N(C_{1-4} aliphatic)$_2$, halogen, C_{1-4} aliphatic, OH, O(C_{1-4} aliphatic), NO_2, CN, CO_2H, CO_2(C_{1-4} aliphatic), O(halo C_{1-4} aliphatic), or halo C_{1-4} aliphatic.

[0026] An aliphatic group or a non-aromatic heterocyclic ring may contain one or more substituents. Suitable substituents on the saturated carbon of an aliphatic group or of a non-aromatic heterocyclic ring are selected from those listed above for the unsaturated carbon of

an aryl or heteroaryl group and the following: =O, =S, =NNHR*, =NN(R*)$_2$, =NNHC(O)R*, =NNHCO$_2$(alkyl), =NNHSO$_2$(alkyl), or =NR*, where each R* is independently selected from hydrogen or an optionally substituted C_{1-6} aliphatic. Optional substituents on the aliphatic group of R* are selected from NH_2, NH(C_{1-4} aliphatic), N(C_{1-4} aliphatic)$_2$, halogen, C_{1-4} aliphatic, OH, O(C_{1-4} aliphatic), NO_2, CN, CO_2H, CO_2(C_{1-4} aliphatic), O(halo C_{1-4} aliphatic), or halo(C_{1-4} aliphatic).

[0027] Optional substituents on the nitrogen of a non-aromatic heterocyclic ring are selected from $-R^+$, $-N(R^+)_2$, $-C(O)R^+$, $-CO_2R^+$, $-C(O)C(O)R^+$, $-C(O)CH_2C(O)R^+$, $-SO_2R^+$, $-SO_2N(R^+)_2$, $-C(=S)N(R^+)_2$, $-C(=NH)-N(R^+)_2$, or $-NR^+SO_2R^+$; wherein R^+ is hydrogen, an optionally substituted C_{1-6} aliphatic, optionally substituted phenyl, optionally substituted -O(Ph), optionally substituted $-CH_2$(Ph), optionally substituted $-CH_2CH_2$(Ph), or an unsubstituted 5-6 membered heteroaryl or heterocyclic ring, or wherein two occurrences of R^+, on the same substituent or different substituents, taken together, form a 5-8-membered heterocyclyl or heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Optional substituents on the aliphatic group or the phenyl ring of R^+ are selected from NH_2, NH(C_{1-4} aliphatic), N(C_{1-4} aliphatic)$_2$, halogen, C_{1-4} aliphatic, OH, O(C_{1-4} aliphatic), NO_2, CN, CO_2H, CO_2(C_{1-4} aliphatic), O(halo C_{1-4} aliphatic), or halo(C_{1-4} aliphatic).

[0028] The term "alkylidene chain" refers to a straight or branched carbon chain that may be fully saturated or have one or more units of unsaturation and has two points of attachment to the rest of the molecule.

[0029] A combination of substituents or variables is permissible only if such a combination results in a stable or chemically feasible compound. A stable compound or chemically feasible compound is one that is not substantially altered when kept at a temperature of 40°C or less, in the absence of moisture or other chemically reactive conditions, for at least a week.

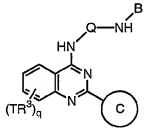
[0030] It will be apparent to one skilled in the art that certain compounds of this invention may exist in tautomeric forms, all such tautomeric forms of the compounds being within the scope of the invention.

[0031] Unless otherwise stated, structures depicted herein are also meant to include all stereochemical forms of the structure; i.e., the R and S configurations for each asymmetric center. Therefore, single stereochemical isomers as well as enantiomeric and diastereomeric mixtures of the present compounds are within the scope of the invention.

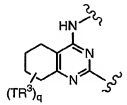
Unless otherwise stated, structures depicted herein are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures except for the replacement of a hydrogen by a deuterium or tritium, or the replacement of a carbon by a ^{13}C- or ^{14}C-enriched carbon are within the scope of this invention. Such compounds are useful, for example, as analytical tools or probes in biological assays.

[0032] *II. Description of Certain Exemplary Compounds:*

[0033] As described generally above, compounds of formula **I** include both monocyclic and bicyclic pyrimidine systems. For example, in certain embodiments, R^X and R^Y may be taken together to form a fused ring, providing a bicyclic ring system. Preferred R^X/R^Y rings include a 5-, 6-, 7-, or 8-membered partially saturated or aromatic ring having 0-2 heteroatoms, wherein said R^X/R^Y ring is optionally substituted with oxo or one or more occurrences of TR^3 or R^4. Examples of certain preferred pyrimidine ring A systems of formula **I** are the mono- and bicyclic ring A systems shown below, wherein B, Q, TR^3, R^4 and ring C are as defined generally above and herein, and q is 0-4.



I-A



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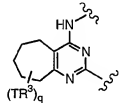

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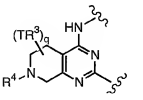

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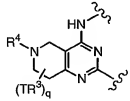

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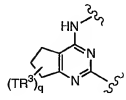

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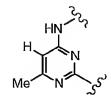

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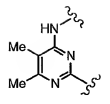
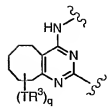
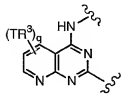


I-H



I-I



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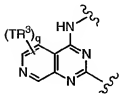

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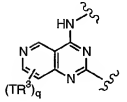

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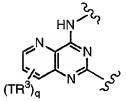

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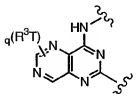

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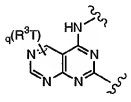
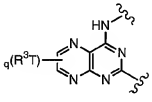
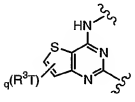


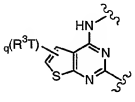
I-O



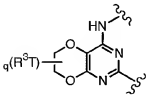
I-P



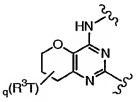
I-Q



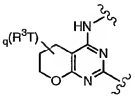
I-R



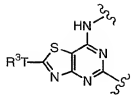
I-S



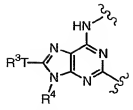
I-T



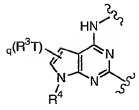
I-U



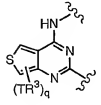
I-V



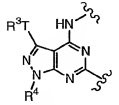
I-W



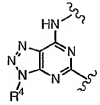
I-X



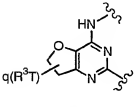
I-Y



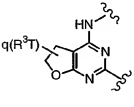
I-Z



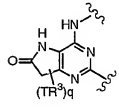
I-AA



I-BB



I-CC



I-DD

[0034] Preferred bicyclic Ring A systems include **I-A**, **I-B**, **I-C**, **I-D**, **I-E**, **I-F**, **I-G**, **I-H**, **I-I**, **I-J**, **I-K**, **I-L**, and **I-M**, more preferably **I-A**, **I-B**, **I-C**, **I-F**, and **I-H**, and most preferably **I-A**, **I-B**, and **I-H**.

[0035] As described generally above, the bicyclic pyrimidine ring system formed when R^X and R^Y are taken together may optionally be substituted with one or more occurrences of $T\text{-}R^3$ on any substitutable carbon atom, and with R^4 on any substitutable nitrogen atom. Exemplary $T\text{-}R^3$ substituents include –R', halo, -OR', -C(=O)R', $-CO_2R'$, -COCOR', $-NO_2$, -CN, $-S(O)R'$, $-SO_2R'$, -SR', $-N(R^4)_2$, $-CON(R^4)_2$, $-SO_2N(R^4)_2$, $-OC(=O)R'$, $-N(R^4)COR'$, $-N(R^4)CO_2$(optionally substituted $C_{1\text{-}6}$ aliphatic), $-N(R^4)N(R^4)_2$, $-C{=}NN(R^4)_2$, -C=N-OR', $-N(R^4)CON(R^4)_2$, $-N(R^4)SO_2N(R^4)_2$, $-N(R^4)SO_2R'$, or $-OC(=O)N(R^4)_2$. Exemplary R^4 substituents include $-R^7$, $-COR^7$, $-CO_2(C_{1\text{-}6}$ aliphatic), $-CON(R^7)_2$, or $-SO_2R^7$, or two R^4 on the same nitrogen are taken together to form a 5-8 membered heterocyclyl or heteroaryl ring, and R' and R^7 are as defined herein. Preferred R^X/R^Y ring substituents include -halo, -R', -OR', -COR', $-CO_2R'$, $-CON(R^4)_2$, -CN, or $-N(R^4)_2$ wherein R' is H or an optionally substituted $C_{1\text{-}6}$ aliphatic group.

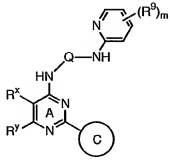
[0036] In certain other exemplary embodiments, compounds of formula I have a monocyclic pyrimidine ring system which is substituted by R^X and R^Y. Preferred R^X groups include hydrogen, alkyl- or dialkylamino, acetamido, or a C_{1-4} aliphatic group such as methyl, ethyl, cyclopropyl, isopropyl or t-butyl. Preferred R^Y groups include T-R^3 wherein T is a valence bond or a methylene, and R^3 is –R', -$N(R^4)_2$, or –OR'. When R^3 is –R' or –OR', a preferred R' is an optionally substituted group selected from C_{1-6} aliphatic, phenyl, or a 5-6 membered heteroaryl or heterocyclyl ring. Examples of preferred R^Y include 2-pyridyl, 4-pyridyl, piperidinyl, methyl, ethyl, cyclopropyl, isopropyl, t-butyl, alkyl- or dialkylamino, acetamido, optionally substituted phenyl such as phenyl or halo-substituted phenyl, and methoxymethyl.

[0037] As described generally above, Q is a C_{1-4} alkylidene chain, wherein each methylene unit of said Q is substituted by R^2 and $R^{2'}$, and up to two non-adjacent methylene units of said Q are optionally and independently replaced by -SO_2 or -C(=O)-. Preferred R^2 and $R^{2'}$ groups include H, alkyl, haloalkyl, heterocycloaminoalkyl, alkylaminoalkyl, and alkyl, wherein all alkyl moieties have 1-10 carbon atoms and are unsubstituted unless otherwise indicated. More preferably, each of R^2 and $R^{2'}$ is hydrogen. In certain preferred embodiments, Q is -CH_2CH_2-, -$CH_2CH_2CH_2$-, or –$CH_2CH_2CH_2CH_2$-, -SO_2CH_2-, -CH_2SO_2-, -(C=O)CH_2-, or –CH_2(C=O)-. In more preferred embodiments, Q is -CH_2CH_2-, -$CH_2CH_2CH_2$-, or –$CH_2CH_2CH_2CH_2$-, -SO_2CH_2-, or -CH_2SO_2-. In most preferred embodiments, Q is -CH_2CH_2-, -$CH_2CH_2CH_2$-, or –$CH_2CH_2CH_2CH_2$-.

[0038] In certain embodiments, B is an optionally substituted carbocyclic aryl having 5-10 carbon ring atoms. In certain other embodients, B is an optionally substituted heteroaryl having 5-10 carbon ring atoms and one or more ring heteroatoms. Preferred B groups include pyridyl, pyrimidinyl, thiazolyl, indolyl, imidazolyl, oxadiazolyl, tetrazolyl, pyrazinyl, triazolyl, thienyl, furanyl, quinolinyl, purinyl, naphthyl, benzothiazolyl, benzopyridyl, benzimidazolyl, indazolyl, isothiazolyl, pyrazolyl, pyridazinyl, isoxazolyl, phenyl, benzothiophenyl, and pyridothiophenyl, all of which may be substituted with at least one and no more than three substituents. Exemplary substituents are independently selected from, without limitation, nitro, amino, cyano, halo, thioamido, amidino, oxamidino, alkoxyamidino, imidino, guanidino, sulfonamido, carboxyl, formyl, alkyl, haloalkyl, alkoxy, haloalkoxy, alkoxyalkyl, alkylaminoalkoxy, alkylcarbonyl, aralkylcarbonyl, heteroaralkylcarbonyl, alkylthio, aminoalkyl, cyanoalkyl, hydroxy, alkoxycarbonyl, aryl,

aralkyl, heteroaryl, and heteroaralkyl, wherein all alkyl moieties have 1-10 carbon atoms and are unsubstituted unless otherwise indicated.

[0039] In other preferred embodiments, B is optionally substituted 2-pyridyl and compounds have the general formula **II**:



II

wherein m is 0-4, and each occurrence of R^9 is independently selected from H, nitro, amino, cyano, halo, thioamido, amidino, oxamidino, alkoxyamidino, imidino, guanidino, sulfonamido, carboxyl, formyl, alkyl, haloalkyl, alkoxy, haloalkoxy, alkoxyalkyl, alkylaminoalkoxy, alkylcarbonyl, aralkylcarbonyl, heteroaralkylcarbonyl, alkylthio, aryl, aralkyl, heteroaryl, and heteroaralkyl, wherein all alkyl moieties have 1-10 carbon atoms and are unsubstituted unless otherwise indicated. In preferred embodiments, m is 0, 1, or 2. In more preferred embodiments, m is 1 or 2. Most preferred R^9 substituents include hydrogen, C_{1-4}alkyl, nitro, amino, cyano, cyanomethyl, trifluoromethyl, hydroxy, and methoxy.

[0040] In other preferred embodiments, B is indazolyl, pyrazolyl, or thiazolyl optionally substituted with one or more independent occurrences of R^9. Preferred R^9 substituents on indazolyl, pyrazolyl, or thiazolyl include hydrogen, C_{1-4}alkyl, nitro, amino, cyano, cyanomethyl, trifluoromethyl, hydroxy, and methoxy.

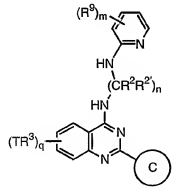
[0041] Preferred formula **I** Ring C groups are phenyl and pyridinyl. When two adjacent substituents on Ring C are taken together to form a fused ring, Ring C is contained in a bicyclic ring system. Preferred fused rings include a benzo or pyrido ring. Such rings preferably are fused at ortho and meta positions of Ring C. Examples of preferred bicyclic Ring C systems include naphthyl, quinolinyl, isoquinolinyl and benzodioxolyl.

[0042] Preferably, Ring C groups have one to two ortho substituents independently selected from R^1. An ortho position on Ring C is defined relative to the position where the pyrimidine ring is attached. Preferred R^1 groups include –halo, an optionally substituted C_{1-}

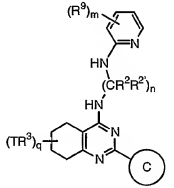
$_6$ aliphatic group, phenyl, -COR^6, -OR^6, -CN, -SO_2R^6, -SO_2NH_2, -$N(R^6)_2$, -CO_2R^6, -$CONH_2$, -$NHCOR^6$, -$OC(O)NH_2$, or -$NHSO_2R^6$. When R^1 is an optionally substituted C_{1-6} aliphatic group, the most preferred optional substituents are halogen. Examples of preferred R^1 groups include $-CF_3$, -Cl, -F, -CN, $-COCH_3$, $-OCH_3$, -OH, $-CH_2CH_3$, $-OCH_2CH_3$, $-CH_3$, $-CF_2CH_3$, cyclohexyl, t-butyl, isopropyl, cyclopropyl, -C≡CH, -C≡C-CH_3, $-SO_2CH_3$, $-SO_2NH_2$, $-N(CH_3)_2$, $-CO_2CH_3$, $-CONH_2$, -$NHCOCH_3$, -$OC(O)NH_2$, -$NHSO_2CH_3$, and $-OCF_3$.

[0043] On Ring C of formula **I**, preferred R^5 substituents, when present, include -halo, -CN, $-NO_2$, $-N(R^4)_2$, optionally substituted C_{1-6} aliphatic group, -OR', -C(O)R', $-CO_2R'$, $-CONH(R^4)$, $-N(R^4)COR'$, $-SO_2N(R^4)_2$, and $-N(R^4)SO_2R'$. More preferred R^5 substituents include -Cl, -F, -CN, $-CF_3$, $-NH_2$, $-NH(C_{1-4}$ aliphatic), $-N(C_{1-4}$ aliphatic$)_2$, $-O(C_{1-4}$ aliphatic), C_{1-4} aliphatic, and $-CO_2(C_{1-4}$ aliphatic). Examples of such preferred R^5 substituents include -Cl, -F, -CN, $-CF_3$, $-NH_2$, -NHMe, $-NMe_2$, -OEt, methyl, ethyl, cyclopropyl, isopropyl, t-butyl, and $-CO_2Et$.

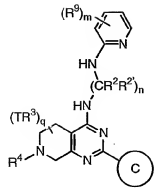
[0044] More preferred ring systems of formula **I** are the following, which may be substituted as described above, wherein B is pyridyl and R^X and R^Y are each methyl, or R^X and R^Y are taken together with the pyrimidine ring to form a quinazoline, tetrahydroquinazoline, or tetrahydropyridopyrimidine ring:



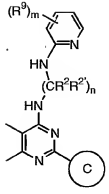
I-A-a



I-B-a



I-D-a



I-H-a

[0045] Particularly preferred are those compounds of formula **I-A-a**, **I-B-a**, **I-D-a**, or **I-H-a**, wherein ring C is a phenyl ring and R^1 is halo, methyl, cyano, OMe, OH, or trifluoromethyl.

[0046] Preferred formula **I** compounds include those compounds where one or more of, or each of, B, ring C, R^X, R^Y, or R^1 is defined such that:

(a) B is an optionally substituted 5-6 membered monocyclic or 8-10 membered bicyclic aromatic ring, wherein said monocyclic or bicyclic ring has 1-4 heteroatoms selected from oxygen, sulfur or nitrogen;

(b) Ring C is a phenyl or pyridinyl ring having one or two ortho substituents independently selected from $-R^1$, wherein Ring C is further substituted by $-R^5$ and wherein when Ring C and two adjacent substituents thereon form a bicyclic ring system, the bicyclic ring system is selected from a naphthyl, quinolinyl or isoquinolinyl ring;

(c) R^X is hydrogen or C_{1-4} aliphatic and R^Y is $T\text{-}R^3$, or R^X and R^Y are taken together with their intervening atoms to form an optionally substituted 5-7 membered partially saturated or aromatic ring having 0-2 ring nitrogens; and

(d) R^1 is –halo, an optionally substituted C_{1-6} aliphatic group, phenyl, $-COR^6$, $-OR^6$, -CN, $-SO_2R^6$, $-SO_2NH_2$, $-N(R^6)_2$, $-CO_2R^6$, $-CONH_2$, $-NHCOR^6$, $-OC(O)NH_2$, or $-NHSO_2R^6$.

[0047] Other preferred formula **I** compounds include those compounds where one or more of, or each of, B, R^2, ring C, R^X, R^Y, R^1, or R^5 is defined such that:

(a) B is an optionally substituted group selected from pyridyl, pyrimidinyl, thiazolyl, indolyl, imidazolyl, oxadiazolyl, tetrazolyl, pyrazinyl, triazolyl, thienyl, furanyl, quinolinyl, purinyl, naphthyl, benzothiazolyl, benzopyridyl, benzimidazolyl, indazolyl,

isothiazolyl, pyrazolyl, pyridazinyl, isoxazolyl, phenyl, benzothiophenyl, or pyridothiophenyl;

(b) R^2 is H, alkyl, haloalkyl, heterocycloaminoalkyl, alkylaminoalkyl, and alkyl, wherein all alkyl moieties have 1-10 carbon atoms are unsubstituted;

(c) Ring C is a phenyl or pyridinyl ring having one or two ortho substituents independently selected from $-R^1$, wherein Ring C is further substituted by $-R^5$ and wherein when Ring C and two adjacent substituents thereon form a bicyclic ring system, the bicyclic ring system is a naphthyl ring;

(d) R^X is hydrogen or methyl and R^Y is –R', $N(R^4)_2$, or –OR', or R^X and R^Y are taken together with their intervening atoms to form a 5-7 membered partially saturated or aromatic carbocyclo ring optionally substituted with –R', halo, -OR', -C(=O)R', $-CO_2R'$, -COCOR', $-NO_2$, -CN, -S(O)R', $-SO_2R'$, -SR', $-N(R^4)_2$, $-CON(R^4)_2$, $-SO_2N(R^4)_2$, $-OC(=O)R'$, $-N(R^4)COR'$, $-N(R^4)CO_2$(optionally substituted C_{1-6} aliphatic), $-N(R^4)N(R^4)_2$, $-C{=}NN(R^4)_2$, -C=N-OR', $-N(R^4)CON(R^4)_2$, $-N(R^4)SO_2N(R^4)_2$, $-N(R^4)SO_2R'$, or $-OC(=O)N(R^4)_2$;

(e) R^1 is –halo, a C_{1-6} haloaliphatic group, a C_{1-6} aliphatic group, phenyl, OMe, OH, or -CN; and

(f) each R^5 is independently selected from -halo, -CN, $-NO_2$, $-N(R^4)_2$, optionally substituted C_{1-6} aliphatic group, -OR', -C(O)R', $-CO_2R'$, $-CONH(R^4)$, $-N(R^4)COR'$, $-SO_2N(R^4)_2$, or $-N(R^4)SO_2R'$.

[0048] Still other preferred formula **I** compounds include those compounds where one or more of, or each of, B, R^2, ring C, R^X, R^Y, R^1, or R^5 is defined such that:

(a) B is an optionally substituted pyridyl group optionally substituted by 0, 1, or 2 occurrences of R^9, wherein each occurrence of R^9 is independently hydrogen, C_{1-4}alkyl, nitro, amino, cyano, cyanomethyl, trifluoromethyl, hydroxy, and methoxy;

(b) R^2 is H, alkyl, haloalkyl, heterocycloaminoalkyl, alkylaminoalkyl, and alkyl, wherein all alkyl moieties have 1-10 carbon atoms are unsubstituted;

(c) Ring C is a phenyl or pyridinyl ring having one or two ortho substituents independently selected from $-R^1$, wherein Ring C is further substituted by $-R^5$ and wherein when Ring C and two adjacent substituents thereon form a bicyclic ring system, the bicyclic ring system is a naphthyl ring;

(d) R^X is hydrogen or methyl and R^Y is –R', $N(R^4)_2$, or –OR', or R^X and R^Y are taken together with their intervening atoms to form a 5-7 membered partially saturated or aromatic ring having 1-2 nitrogen ring atoms optionally substituted with –R', halo, -OR', -C(=O)R', $-CO_2R'$, -COCOR', $-NO_2$, -CN, -S(O)R', $-SO_2R'$, -SR', $-N(R^4)_2$, $-CON(R^4)_2$, $-SO_2N(R^4)_2$, $-OC(=O)R'$, $-N(R^4)COR'$, $-N(R^4)CO_2$(optionally substituted C_{1-6} aliphatic), $-N(R^4)N(R^4)_2$, $-C=NN(R^4)_2$, -C=N-OR', $-N(R^4)CON(R^4)_2$, $-N(R^4)SO_2N(R^4)_2$, $-N(R^4)SO_2R'$, or $-OC(=O)N(R^4)_2$;

(e) R^1 is –halo, a C_{1-6} haloaliphatic group, a C_{1-6} aliphatic group, phenyl, OMe, OH, or -CN; and

(f) each R^5 is independently selected from -halo, -CN, $-NO_2$, $-N(R^4)_2$, optionally substituted C_{1-6} aliphatic group, -OR', $-C(O)R'$, $-CO_2R'$, $-CONH(R^4)$, $-N(R^4)COR'$, $-SO_2N(R^4)_2$, or $-N(R^4)SO_2R'$.

[0049] Even more preferred formula **I** compounds include those compounds where one or more of, or each of, B, R^2, ring C, R^X, R^Y, R^1, or R^5 is defined such that:

(a) B is an optionally substituted pyridyl group optionally substituted with 2 independent occurrences of R^9, wherein each occurrence of R^9 is independently hydrogen, C_{1-4}alkyl, nitro, amino, cyano, cyanomethyl, trifluoromethyl, hydroxy, and methoxy;

(b) each R^2 and $R^{2'}$ is H;

(c) Ring C is a phenyl ring having one or two ortho substituents independently selected from $-R^1$, wherein Ring C is further substituted by $-R^5$;

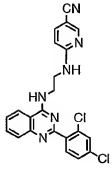
(d) R^X is hydrogen or methyl and R^Y is methyl, methoxymethyl, ethyl, cyclopropyl, isopropyl, t-butyl, alkyl- or an optionally substituted group selected from 2-pyridyl, 4-pyridyl, piperidinyl, or phenyl, or R^X and R^Y are taken together with their intervening atoms to form an optionally substituted benzo ring or partially saturated 6-membered carbocyclo ring;

(e) R^1 is –halo, a C_{1-4} aliphatic group optionally substituted with halogen, OMe, OH, or -CN; and

(f) each R^5 is independently selected from -Cl, -F, -CN, $-CF_3$, $-NH_2$, $-NH(C_{1-4}$ aliphatic), $-N(C_{1-4}$ aliphatic$)_2$, $-O(C_{1-4}$ aliphatic), optionally substituted C_{1-4} aliphatic, and $-CO_2(C_{1-4}$ aliphatic).

[0050] Representative compounds of formula **I** are shown below in Table 1.

Table 1



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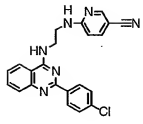

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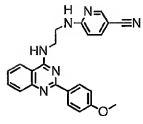

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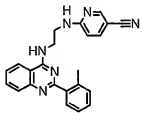

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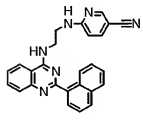

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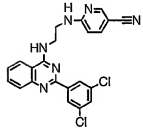

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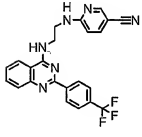

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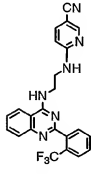

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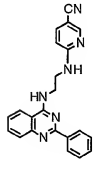

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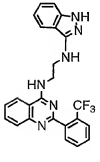

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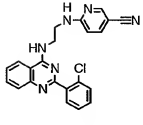

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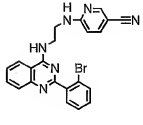

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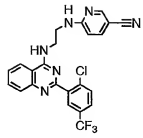

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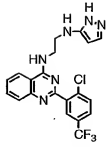

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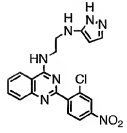

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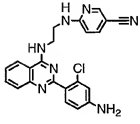

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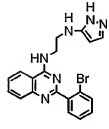

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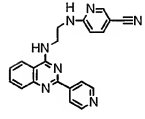

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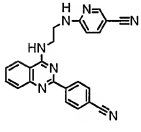

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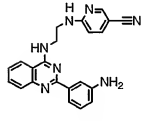

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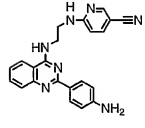

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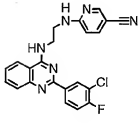

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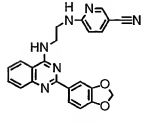

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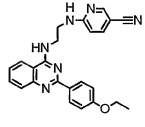

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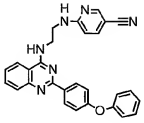

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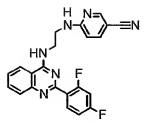

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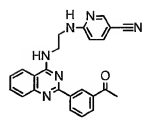

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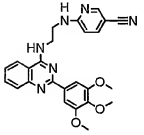

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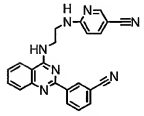

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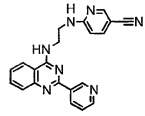

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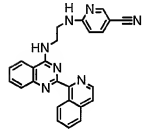

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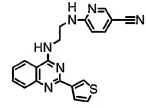

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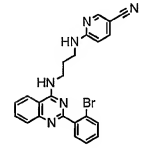

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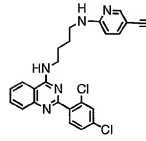

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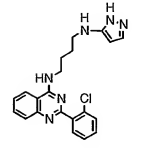

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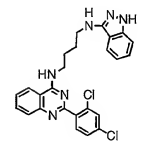

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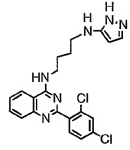

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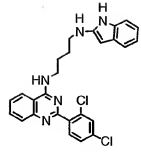

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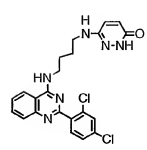

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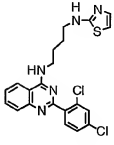

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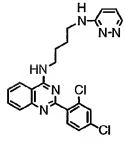

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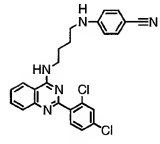

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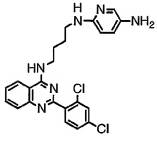

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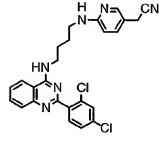

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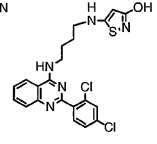

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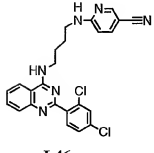

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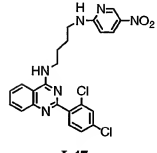

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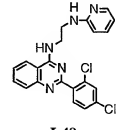

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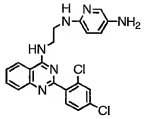

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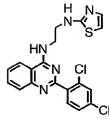

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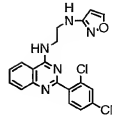

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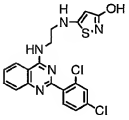

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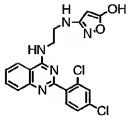

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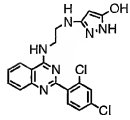

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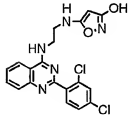

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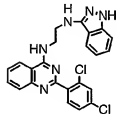

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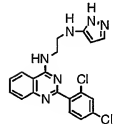

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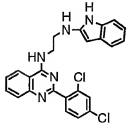

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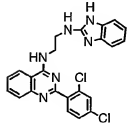

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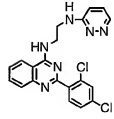

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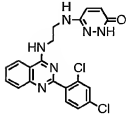

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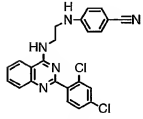

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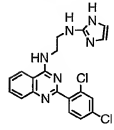

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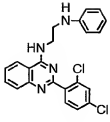

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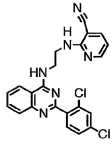

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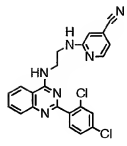

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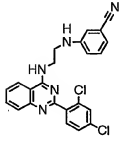

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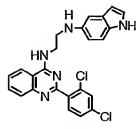

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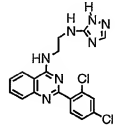

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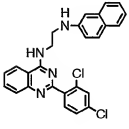

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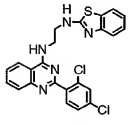

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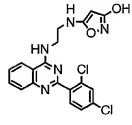

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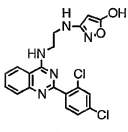

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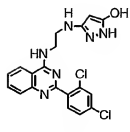

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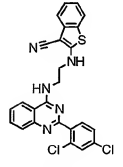

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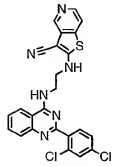

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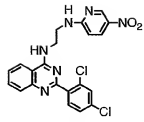

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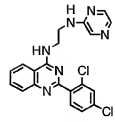

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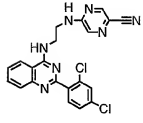

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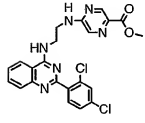

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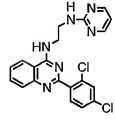

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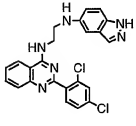

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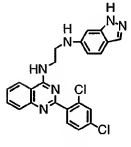

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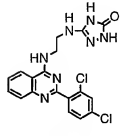

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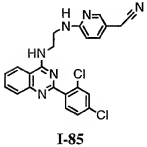

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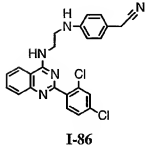

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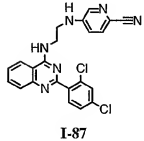

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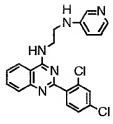

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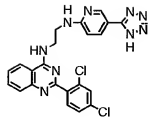

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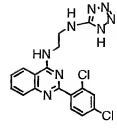

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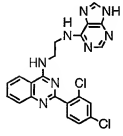

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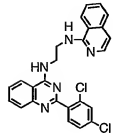

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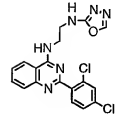

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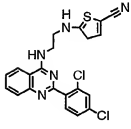

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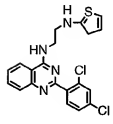

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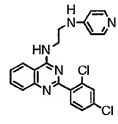

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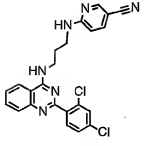

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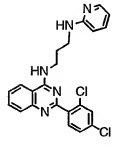

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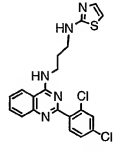

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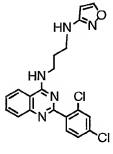

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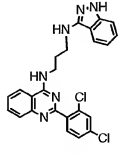

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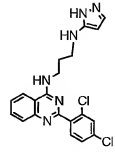
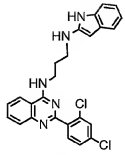
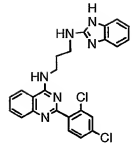


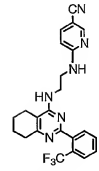
I-102



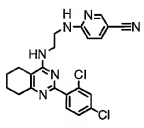
I-103



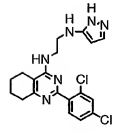
I-104



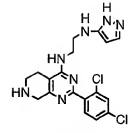
I-105



I-106



I-107



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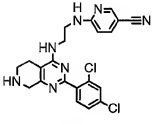
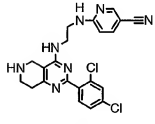


I-109



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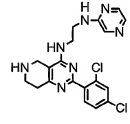

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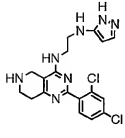
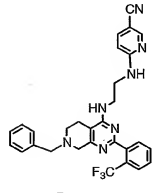
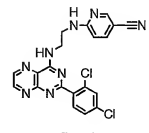


I-112



I-113



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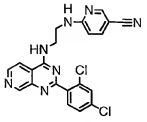

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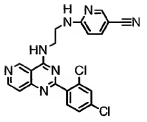

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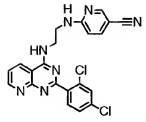

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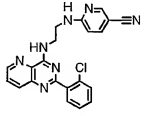

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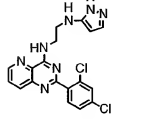

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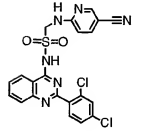

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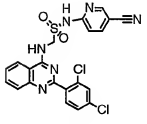

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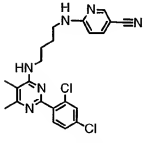

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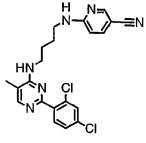

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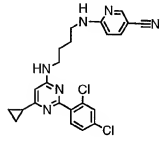

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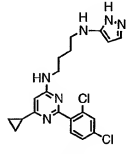

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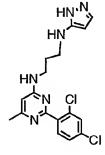

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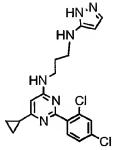

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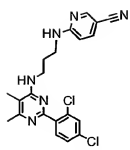

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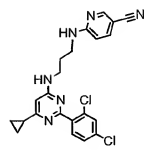

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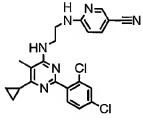

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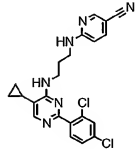

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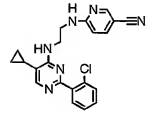

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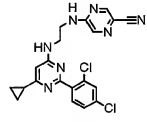

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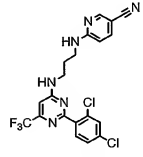

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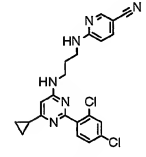

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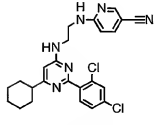

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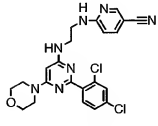

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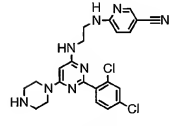

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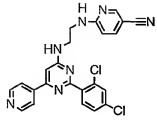

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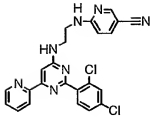

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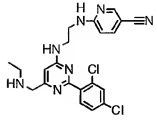

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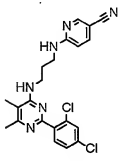

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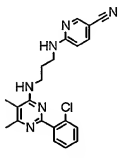

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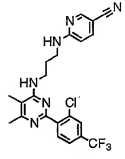

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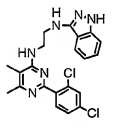

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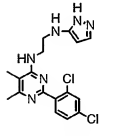

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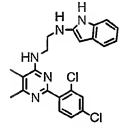

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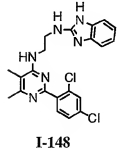

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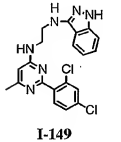

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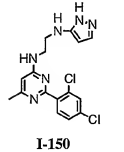

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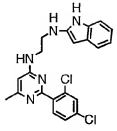

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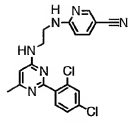

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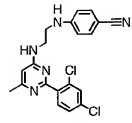
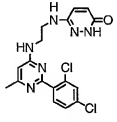
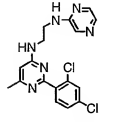


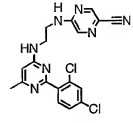
I-153



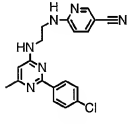
I-154



I-155



I-156



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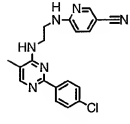
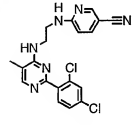
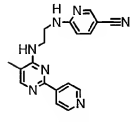


I-158



I-159



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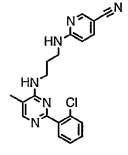

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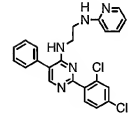

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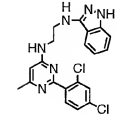

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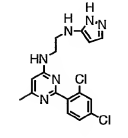

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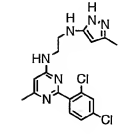

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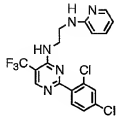

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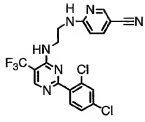

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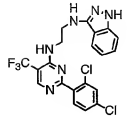

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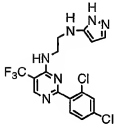

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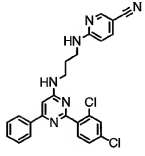

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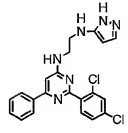

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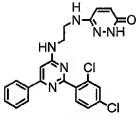

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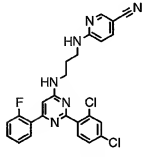

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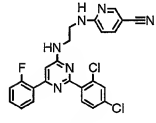

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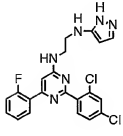

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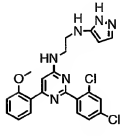

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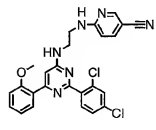

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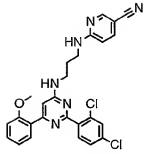

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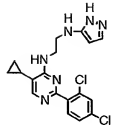

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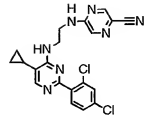

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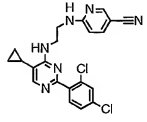

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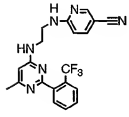

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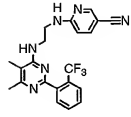

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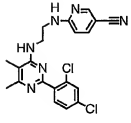

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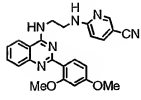

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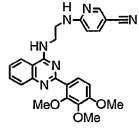

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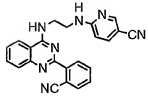

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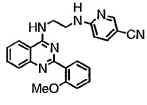

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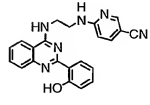

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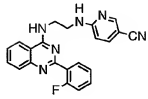

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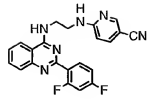

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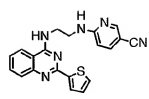

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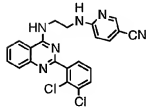

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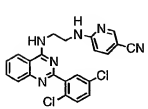

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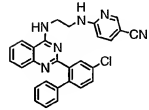

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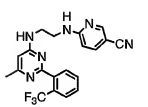

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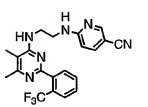

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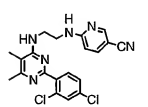

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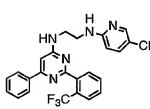

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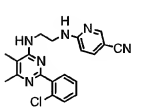

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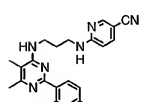

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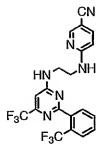

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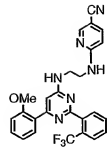


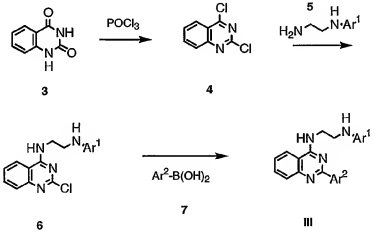
I-203

[0051] *III. General Synthetic Methodology:*

[0052] The compounds of this invention may be prepared in general by methods known to those skilled in the art for analogous compounds, as illustrated by the general scheme below, and the preparative examples that follow.

[0053] Although certain exemplary embodiments are depicted and described above and herein, it will be appreciated that a compounds of the invention can be prepared according to the methods described generally above using appropriate starting materials.

[0054] **Scheme I**



[0055] Scheme I shows a general approach for making compounds of formula **III**. In Scheme I, Ar^1 is a synthetic equivalent of B in formula **I** and Ar^2 is a synthetic equivalent of Ring C in formula **I**. Preparation of the dichloropyrimidine **4** may be achieved in a manner similar to that described in *Chem. Pharm. Bull.*, **30**, 3121-3124 (1982). The chlorine in position 4 of intermediate **4** may be replaced by a diamine **5** to provide intermediate **6** in a manner similar to that described in *J. Med. Chem.*, **38**, 3547-3557 (1995). The diamine **5** may be either commercially available, readily synthesized via methods known in the art

such as those described in WO 99/65897 (Chiron), or provided by methods disclosed in the synthetic examples. Although an example where Q is $-CH_2CH_2-$ is depicted above, it will be appreciated that additional compounds where Q is described generally for formula **I** can also be prepared according to the methods cited above. Ring C is then introduced using a boronic ester **7** under palladium catalysis [see *Tetrahedron*, **48**, 8117-8126 (1992)]. This method is illustrated by the following procedure.

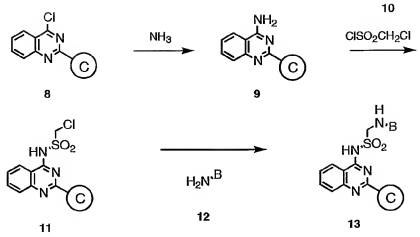
[0056] A suspension of 1*H*-quinazoline-2,4-dione **3** (10.0 g, 61.7 mmol) in $POCl_3$ (60 mL, 644 mmol) and N,N-dimethylaniline (8mL, 63.1 mmol) is heated under reflux for 2 h. Excess $POCl_3$ is evaporated under vacuum, the residue is poured into ice, and the precipitate is collected by filtration. The crude solid 2,4-dichloroquinazoline product **4** may be used without further purification.

[0057] To a solution of 2,4-dichloro-quinazoline **4** (3.3 g, 16.6 mmol) in anhydrous ethanol (150 mL) is added a diamine **5** (32.9 mmol). The mixture is stirred at room temperature for 4 hours, and the resulting precipitate is collected by filtration, washed with ethanol, and dried under vacuum to afford intermediate **6**.

[0058] To a solution of intermediate **6** (0.19 mmol) in DMF (1.0 mL) is added the desired boronic acid **7** (0.38 mmol), 2M Na_2CO_3 (0.96 mmol), and tri-t-butylphosphine (0.19 mmol). Under nitrogen, $PdCl_2$(dppf) (0.011 mmol) is added in one portion. The reaction mixture is then heated at 80°C for 5 to 10 hours, cooled to room temperature, and poured into water (2 mL). The resulting precipitate is collected by filtration, washed with water, and purified by HPLC.

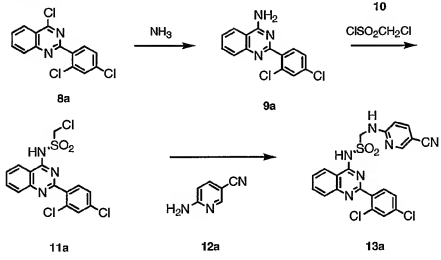
[0059] Compounds where one methylene unit of Q is replaced by SO_2 can be prepared according to the general methods depicted in Schemes 2, 3, 4 and 5 below. Scheme 2 illustrates a general method for the preparation of compounds of formula **13**. Although compounds where Ring A is quinazolinyl are depicted below, it will be appreciated that compounds of general formula **I** (for example compounds having other ring systems as described generally herein) can also be prepared according to these methods.

[0060] Scheme 2



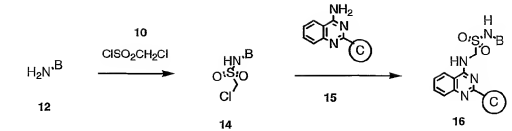
[0061] Scheme 3 depicts the preparation of certain exemplary compounds where ring C is a substituted phenyl moiety, and B is a substituted pyridyl moiety.

[0062] **Scheme 3**



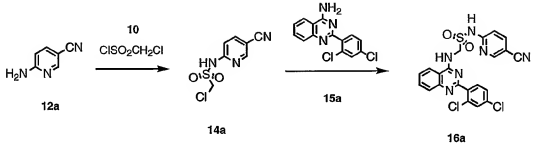
[0063] Scheme 4 illustrates a general method for the preparation of compounds of formula **16**. Although compounds where Ring A is quinazolinyl are depicted below, it will be appreciated that compounds of general formula **I** (for example compounds having other ring systems as described generally herein) can also be prepared according to these methods.

[0064] **Scheme 4**



[0065] Scheme 5 depicts the preparation of certain exemplary compounds where ring C is a substituted phenyl moiety, and B is a substituted pyridyl moiety.

[0066] **Scheme 5**



[0067] One having ordinary skill in the art may synthesize other compounds of this invention following the teachings of the specification using reagents that are readily synthesized or commercially available.

[0068] *IV. Uses of Compounds of the Invention:*

[0069] The activity of a compound utilized in this invention as an inhibitor of GSK-3 kinase may be assayed *in vitro, in vivo* or in a cell line according to methods known in the art. *In vitro* assays include assays that determine inhibition of either the phosphorylation activity or ATPase activity of activated GSK-3. Alternate *in vitro* assays quantitate the ability of the inhibitor to bind to GSK-3. Inhibitor binding may be measured by radiolabelling the inhibitor prior to binding, isolating the inhibitor/GSK-3 complex and determining the amount of radiolabel bound. Alternatively, inhibitor binding may be determined by running a competition experiment where new inhibitors are incubated with GSK-3 bound to known radioligands. Detailed conditions for assaying a compound utilized in this invention as an inhibitor of GSK-3 kinase are set forth in the Examples below.

[0070] According to another embodiment, the invention provides a composition comprising a compound of this invention or a pharmaceutically acceptable derivative thereof and a pharmaceutically acceptable carrier, adjuvant, or vehicle. Preferably, the amount of compound in the compositions of this invention is such that is therapeutically

effective, and most preferably effective to detectably inhibit a protein kinase, particularly GSK-3 kinase, in a biological sample or in a patient. Preferably the composition of this invention is formulated for administration to a patient in need of such composition. Most preferably, the composition of this invention is formulated for oral administration to a patient.

[0071] The term "patient", as used herein, means an animal, preferably a mammal, and most preferably a human.

[0072] The term "pharmaceutically acceptable carrier, adjuvant, or vehicle" refers to a non-toxic carrier, adjuvant, or vehicle that does not destroy the pharmacological activity of the compound with which it is formulated. Pharmaceutically acceptable carriers, adjuvants or vehicles that may be used in the compositions of this invention include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat.

[0073] The term "detectably inhibit", as used herein means a measurable change in GSK-3 activity between a sample comprising said composition and a GSK-3 kinase and an equivalent sample comprising GSK-3 kinase in the absence of said composition.

[0074] Pharmaceutically acceptable salts of the compounds of this invention include those derived from pharmaceutically acceptable inorganic and organic acids and bases. Examples of suitable acid salts include acetate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptanoate, glycerophosphate, glycolate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oxalate, palmoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, salicylate, succinate, sulfate, tartrate, thiocyanate, tosylate and undecanoate. Other acids, such as oxalic, while not in themselves pharmaceutically acceptable, may be employed in

the preparation of salts useful as intermediates in obtaining the compounds of the invention and their pharmaceutically acceptable acid addition salts.

[0075] Salts derived from appropriate bases include alkali metal (e.g., sodium and potassium), alkaline earth metal (e.g., magnesium), ammonium and $N^+(C_{1-4}$ alkyl$)_4$ salts. This invention also envisions the quaternization of any basic nitrogen-containing groups of the compounds disclosed herein. Water or oil-soluble or dispersible products may be obtained by such quaternization.

[0076] The compositions of the present invention may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir. The term "parenteral" as used herein includes subcutaneous, intravenous, intramuscular, intra-articular, intra-synovial, intrasternal, intrathecal, intrahepatic, intralesional and intracranial injection or infusion techniques. Preferably, the compositions are administered orally, intraperitoneally or intravenously. Sterile injectable forms of the compositions of this invention may be aqueous or oleaginous suspension. These suspensions may be formulated according to techniques known in the art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium.

[0077] For this purpose, any bland fixed oil may be employed including synthetic mono- or di-glycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant, such as carboxymethyl cellulose or similar dispersing agents that are commonly used in the formulation of pharmaceutically acceptable dosage forms including emulsions and suspensions. Other commonly used surfactants, such as Tweens, Spans and other emulsifying agents or bioavailability enhancers which are commonly used in the manufacture of pharmaceutically acceptable solid, liquid, or other dosage forms may also be used for the purposes of formulation.

[0078] The pharmaceutically acceptable compositions of this invention may be orally administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, aqueous suspensions or solutions. In the case of tablets for oral use, carriers commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried cornstarch. When aqueous suspensions are required for oral use, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening, flavoring or coloring agents may also be added.

[0079] Alternatively, the pharmaceutically acceptable compositions of this invention may be administered in the form of suppositories for rectal administration. These can be prepared by mixing the agent with a suitable non-irritating excipient that is solid at room temperature but liquid at rectal temperature and therefore will melt in the rectum to release the drug. Such materials include cocoa butter, beeswax and polyethylene glycols.

[0080] The pharmaceutically acceptable compositions of this invention may also be administered topically, especially when the target of treatment includes areas or organs readily accessible by topical application, including diseases of the eye, the skin, or the lower intestinal tract. Suitable topical formulations are readily prepared for each of these areas or organs.

[0081] Topical application for the lower intestinal tract can be effected in a rectal suppository formulation (see above) or in a suitable enema formulation. Topically-transdermal patches may also be used.

[0082] For topical applications, the pharmaceutically acceptable compositions may be formulated in a suitable ointment containing the active component suspended or dissolved in one or more carriers. Carriers for topical administration of the compounds of this invention include, but are not limited to, mineral oil, liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene, polyoxypropylene compound, emulsifying wax and water. Alternatively, the pharmaceutically acceptable compositions can be formulated in a suitable lotion or cream containing the active components suspended or dissolved in one or more pharmaceutically acceptable carriers. Suitable carriers include, but are not limited to, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water.

[0083] For ophthalmic use, the pharmaceutically acceptable compositions may be formulated as micronized suspensions in isotonic, pH adjusted sterile saline, or, preferably,

as solutions in isotonic, pH adjusted sterile saline, either with or without a preservative such as benzylalkonium chloride. Alternatively, for ophthalmic uses, the pharmaceutically acceptable compositions may be formulated in an ointment such as petrolatum.

[0084] The pharmaceutically acceptable compositions of this invention may also be administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other conventional solubilizing or dispersing agents.

[0085] Most preferably, the pharmaceutically acceptable compositions of this invention are formulated for oral administration.

[0086] The amount of the compounds of the present invention that may be combined with the carrier materials to produce a composition in a single dosage form will vary depending upon the host treated, the particular mode of administration. Preferably, the compositions should be formulated so that a dosage of between 0.01-100 mg/kg body weight/day of the inhibitor can be administered to a patient receiving these compositions.

[0087] It should also be understood that a specific dosage and treatment regimen for any particular patient will depend upon a variety of factors, including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, rate of excretion, drug combination, and the judgment of the treating physician and the severity of the particular disease being treated. The amount of a compound of the present invention in the composition will also depend upon the particular compound in the composition.

[0088] Depending upon the particular condition, or disease, to be treated or prevented, additional therapeutic agents, which are normally administered to treat or prevent that condition, may also be present in the compositions of this invention. As used herein, additional therapeutic agents that are normally administered to treat or prevent a particular disease, or condition, are known as "appropriate for the disease, or condition, being treated".

[0089] For example, chemotherapeutic agents or other anti-proliferative agents may be combined with the compounds of this invention to treat proliferative diseases and cancer. Examples of known chemotherapeutic agents include, but are not limited to, Gleevec™, adriamycin, dexamethasone, vincristine, cyclophosphamide, fluorouracil, topotecan, taxol, interferons, and platinum derivatives.

[0090] Other examples of agents the inhibitors of this invention may also be combined with include, without limitation: treatments for Alzheimer's Disease such as Aricept® and Excelon®; treatments for Parkinson's Disease such as L-DOPA/carbidopa, entacapone, ropinrole, pramipexole, bromocriptine, pergolide, trihexephendyl, and amantadine; agents for treating Multiple Sclerosis (MS) such as beta interferon (e.g., Avonex® and Rebif®), Copaxone®, and mitoxantrone; treatments for asthma such as albuterol and Singulair®; agents for treating schizophrenia such as zyprexa, risperdal, seroquel, and haloperidol; anti-inflammatory agents such as corticosteroids, TNF blockers, IL-1 RA, azathioprine, cyclophosphamide, and sulfasalazine; immunomodulatory and immunosuppressive agents such as cyclosporin, tacrolimus, rapamycin, mycophenolate mofetil, interferons, corticosteroids, cyclophophamide, azathioprine, and sulfasalazine; neurotrophic factors such as acetylcholinesterase inhibitors, MAO inhibitors, interferons, anti-convulsants, ion channel blockers, riluzole, and anti-Parkinsonian agents; agents for treating cardiovascular disease such as beta-blockers, ACE inhibitors, diuretics, nitrates, calcium channel blockers, and statins; agents for treating liver disease such as corticosteroids, cholestyramine, interferons, and anti-viral agents; agents for treating blood disorders such as corticosteroids, anti-leukemic agents, and growth factors; agents for treating immunodeficiency disorders such as gamma globulin; and agents for treating diabetes such as insulin or insulin analogues, in injectable or inhalation form, glitazones, alpha glucosidase inhibitors, biguanides, insulin sensitizers, and sulfonyl ureas.

[0091] The amount of additional therapeutic agent present in the compositions of this invention will be no more than the amount that would normally be administered in a composition comprising that therapeutic agent as the only active agent. Preferably the amount of additional therapeutic agent in the presently disclosed compositions will range from about 50% to 100% of the amount normally present in a composition comprising that agent as the only therapeutically active agent.

[0092] In an alternate embodiment, the methods of this invention that utilize compositions that do not contain an additional therapeutic agent, comprise the additional step of separately administering to said patient an additional therapeutic agent. When these additional therapeutic agents are administered separately they may be administered to the patient prior to, sequentially with or following administration of the compositions of this invention.

[0093] According to another embodiment, the invention relates to a method of inhibiting GSK-3 kinase activity in a biological sample comprising the step of contacting said biological sample with a compound of this invention, or a composition comprising said compound.

[0094] The term "biological sample", as used herein, includes, without limitation, cell cultures or extracts thereof; biopsied material obtained from a mammal or extracts thereof; and blood, saliva, urine, feces, semen, tears, or other body fluids or extracts thereof.

[0095] Inhibition of GSK-3 kinase activity in a biological sample is useful for a variety of purposes that are known to one of skill in the art. Examples of such purposes include, but are not limited to, blood transfusion, organ-transplantation, biological specimen storage, and biological assays.

[0096] According to another embodiment, the invention provides a method for treating or lessening the severity of a GSK-3-mediated disease or condition in a patient comprising the step of administering to said patient a composition according to the present invention.

[0097] The term "GSK-3-mediated disease" as used herein, means any disease or other deleterious condition or disease in which GSK-3 is known to play a role. Such diseases or conditions include, without limitation, autoimmune diseases, inflammatory diseases, metabolic, neurological and neurodegenerative diseases, cardiovascular diseases, allergy, asthma, diabetes, Alzheimer's disease, Huntington's disease, Parkinson's disease, AIDS-associated dementia, amyotrophic lateral sclerosis (AML, Lou Gehrig's disease), multiple sclerosis (MS), schizophrenia, cardiomyocyte hypertrophy, reperfusion/ischemia, stroke, and baldness.

[0098] According to a preferred embodiment, the method of the present invention relates to treating or lessening the severity of stroke.

[0099] According to another preferred embodiment, the method of the present invention relates to treating or lessening the severity of a neurodegenerative or neurological disorder.

[00100] In other embodiments, the invention relates to a method of enhancing glycogen synthesis and/or lowering blood levels of glucose in a patient in need thereof, comprising administering to said patient a therapeutically effective amount of a composition comprising a compound of formula **I**. This method is especially useful for diabetic patients.

[00101] In yet another embodiment, the invention relates to a method of inhibiting the production of hyperphosphorylated Tau protein in a patient in need thereof, comprising administering to said patient a therapeutically effective amount of a composition comprising

a compound of formula **I**. This method is especially useful in halting or slowing the progression of Alzheimer's disease.

[00102] In still another embodiments, the invention relates to a method of inhibiting the phosphorylation of β-catenin in a patient in need thereof, comprising administering to said patient a therapeutically effective amount of a composition comprising a compound of formula **I**. This method is especially useful for treating schizophrenia.

[00103] The compounds of this invention or pharmaceutically acceptable compositions thereof may also be incorporated into compositions for coating an implantable medical device, such as prostheses, artificial valves, vascular grafts, stents and catheters. Vascular stents, for example, have been used to overcome restenosis (re-narrowing of the vessel wall after injury). However, patients using stents or other implantable devices risk clot formation or platelet activation. These unwanted effects may be prevented or mitigated by pre-coating the device with a pharmaceutically acceptable composition comprising a kinase inhibitor. Suitable coatings and the general preparation of coated implantable devices are described in US Patents 6,099,562; 5,886,026; and 5,304,121. The coatings are typically biocompatible polymeric materials such as a hydrogel polymer, polymethyldisiloxane, polycaprolactone, polyethylene glycol, polylactic acid, ethylene vinyl acetate, and mixtures thereof. The coatings may optionally be further covered by a suitable topcoat of fluorosilicone, polysaccarides, polyethylene glycol, phospholipids or combinations thereof to impart controlled release characteristics in the composition. Implantable devices coated with a compound of this invention are another embodiment of the present invention.

[00104] In order that the invention described herein may be more fully understood, the following examples are set forth. It should be understood that these examples are for illustrative purposes only and are not to be construed as limiting this invention in any manner.

SYNTHETIC EXAMPLES

[00105] The following HPLC methods were used in the analysis of the compounds as specified in the Synthetic Examples set forth below.

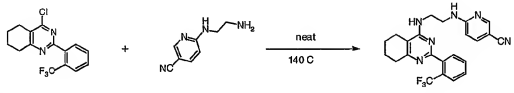
[00106] HPLC conditions

[00107] A)LC-MS: Column: Waters (YMC) ODS-AQ 2.0x50mm, S5, 120A.

Gradient: 90% water (0.2% Formic acid), 10% acetonitrile (containing 0.1% Formic acid) to 10% water (0.1% formic acid), 90% acetonitrile (containing 0.1% formic acid) over 5.0 min, hold for 0. min and return to initial conditions. Total run time 7.0 min. Flow rate: 1.0 mL/min

[00108] HPLC: Column: C18, 3 um, 2.1 X 50 mm, "Lighting" by Jones Chromatography. Gradient: 100% water (containing 1% acetonitrile, 0.1% TFA) to 100% acetonitrile (containing 0.1% TFA) over 4.0 min, hold at 100% acetonitrile for 1.4 min and return to initial conditions. Total run time 7.0

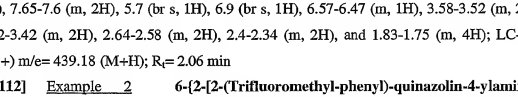
[00109] Example 1 **6-{2-[2-(2-Trifluoromethyl-phenyl)-5,6,7,8-tetrahydro-quinazolin-4-ylamino]-ethylamino}-nicotinonitrile** (Compound I-105)



[00110] A mixture of 4-chloro-2-(2-trifluoromethyl-phenyl)-5,6,7,8-tetrahydro-quinazoline and 6-(2-amino-ethylamino)-nicotinonitrile (prepared according to the method described by Nuss *et al*, WO 99/65997) was dissolved in ethanol (2 mL). The solvent was removed under a stream of nitrogen gas and the residue was heated at 140°C for 18 hours. Purification was achieved by silica gel chromatography (1:1 hexane/ethyl acetate, 1:2 hexane/ethyl acetate) to yield the title compound as a white solid (35 mg, 50%).

[00111] ^{1}H NMR (500 MHz, d_6-DMSO, ppm) δ8.35 (s, 1H), 7.8 (d, 1H), 7.73-7.65 (m, 2H), 7.65-7.6 (m, 2H), 5.7 (br s, 1H), 6.9 (br s, 1H), 6.57-6.47 (m, 1H), 3.58-3.52 (m, 2H), 3.52-3.42 (m, 2H), 2.64-2.58 (m, 2H), 2.4-2.34 (m, 2H), and 1.83-1.75 (m, 4H); LC-MS (ES+) m/e= 439.18 (M+H); R_t= 2.06 min

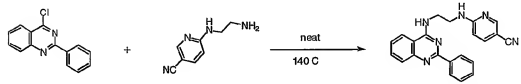
[00112] Example 2 **6-[2-[2-(Trifluoromethyl-phenyl)-quinazolin-4-ylamino]-ethylamino}-nicotinonitrile** (Compound I-8)



[00113] This compound was prepared in an analogous manner as described in Example 1 using 4-chloro-2-(2-trifluoromethyl-phenyl)-quinazoline. Purification was achieved by silica gel chromatography (1:1 hexane/ethyl acetate, 1:2 hexane/ethyl acetate) to yield the title compound (34 mg, 49%).

[00114] ^{1}H NMR (500 MHz, d_6-DMSO, ppm) δ8.58 (br s, 1H), 8.37 (s, 1H), 8.28 (d, 1H), 7.85-7.74 (m, 6H), 7.7-7.66 (m, 1H), 7.6-7.55 (m, 2H), 6.53 (br s, 1H), 3.77-3.72 (m, 2H), 3.65-3.57 (m, 2H); LC-MS (ES+) m/e= 435.09 (M+H); R_t= 2.09 min.

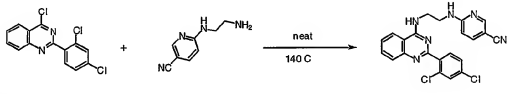
[00115] Example 3 **6-[2-(2-Phenyl-quinazolin-4-ylamino)-ethylamino]-nicotinonitrile** (Compound I-9)



[00116] This compound was prepared in an analogous manner as described in Example 1 using 4-chloro-2-phenyl-quinazoline. Purification was achieved by silica gel chromatography (2:1 hexane/ethyl acetate, 1:1 hexane/ethyl acetate) to yield the title compound as a white solid (37 mg, 49%).

[00117] ^{1}H NMR (500 MHz, d_6-DMSO, ppm) δ8.52-8.4 (m, 4H), 8.23 (d, 1H), 7.88-7.82 (m, 1H), 7.78-7.71 (m, 2H), 7.66-7.6 (m, 1H), 7.52-7.43 (m, 4H), 6.58-6.49 (m, 1H), 3.9-3.84 (m, 2H), 3.83-3.65 (m, 2H); LC-MS (ES+) m/e= 367.08 (M+H); R_t= 1.91 min.

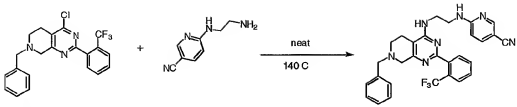
[00118] Example 4 **6-{2-[2-(2,4-Dichloro-phenyl)-quinazolin-4-ylamino]-ethylamino}-nicotinonitrile** (Compound I-1)



[00119] This compound was prepared in an analogous manner as described in Example 1 using 4-chloro-2-(2,4-dichloro-phenyl)-quinazoline and 6-(2-amino-ethylamino)-nicotinonitrile. Purification was achieved by silica gel chromatography (2:1 hexane/ethyl acetate, 1:1 hexane/ethyl acetate) to yield the title compound as a white solid (36 mg, 51%).

[00120] ^{1}H NMR (500 MHz, d_6-DMSO, ppm) δ8.64-8.56 (m, 1H), 8.37 (s, 1H), 8.31-8.24 (m, 1H), 7.84-7.69 (m, 5H), 7.62-7.50 (m, 3H), 6.59-6.48 (m, 1H), 3.80-3.70 (m, 2H), 3.72-3.59 (m, 2H); LC-MS (ES+) m/e= 434.96 (M+H); R_t= 2.18 min.

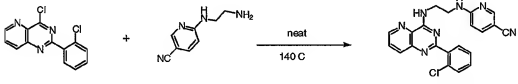
[00121] Example 5 **6-{2-[7-Benzyl-2-(2-trifluoromethyl-phenyl)-5,6,7,8-tetrahydro-pyrido[3,4-*d*]pyrimidin-4-ylamino]-ethylamino}-nicotinonitrile** (Compound I-113)



[00122] This compound was prepared in an analogous manner as described in Example 1 using 7-benzyl-4-chloro-2-(2-trifluoromethyl-phenyl)-5,6,7,8-tetrahydro-pyrido[3,4-*d*]pyrimidine and 6-(2-amino-ethylamino)-nicotinonitrile. Purification was achieved by silica gel chromatography (1:3 hexane/ethyl acetate, 1:4 hexane/ethyl acetate) to yield the title compound as a yellow foam (76 mg, 58%).

[00123] ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ8.30 (s, 1H), 7.75 (d, 1H), 7.69-7.65 (m, 1H), 7.62 (t, 1H), 7.60-7.52 (m, 1H), 7.43-7.27 (m, 6H), 6.11-5.98 (m, 2H), 5.33 (br s, 1H), 3.84-3.73 (m, 4H), 3.66-3.57 (m, 4H), 2.92-2.82 (m, 2H), 2.53-2.42 (m, 2H); LC-MS (ES+) m/e= 530.05 (M+H); R_t= 2.29 min.

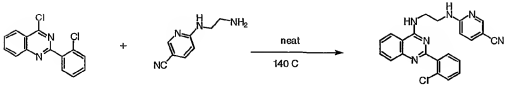
[00124] Example 6 **6-{2-[2-(2-Chloro-phenyl)-pyrido[3,2-*d*]pyrimidin-4-ylamino]-ethylamino}-nicotinonitrile** (Compound I-118)



[00125] This compound was prepared in an analogous manner as described in Example 1 using 4-chloro-2-(2-chloro-phenyl)-pyrido[3,2-*d*]pyrimidine and 6-(2-amino-ethylamino)-nicotinonitrile. Purification was achieved by silica gel chromatography (1:1 hexane/ethyl acetate, 1:2 hexane/ethyl acetate, 1:4 hexane/ethyl acetate) to yield the title compound as a white solid (36 mg, 49%).

[00126] ^{1}H NMR (500 MHz, d_6-DMSO, ppm) δ8.89-8.80 (m, 2H), 8.34 (s, 1H), 8.15 (d, 1H), 7.90-7.82 (m, 1H), 7.80-7.73 (m, 1H), 7.64 (d, 1H), 7.59-7.51 (m, 2H), 7.50-7.40 (m, 2H), 6.59-6.42 (br m, 1H), 3.80-3.75 (m, 2H), 3.70-3.58 (m, 2H); LC-

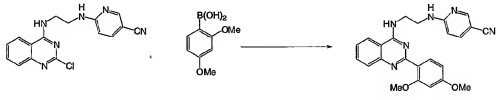
[00127] Example 7 **6-{2-[2-(2-Chloro-phenyl)-quinazolin-4-ylamino]-ethylamino}-nicotinonitrile** (Compound I-11)



[00128] This compound was prepared in an analogous manner as described in Example 1 using 4-chloro-2-(2-chloro-phenyl)-quinazoline. Purification was achieved by silica gel chromatography (1:1 hexane/ethyl acetate, 1:2 hexane/ethyl acetate)to yield the title compound as a white solid (47 mg, 64%).

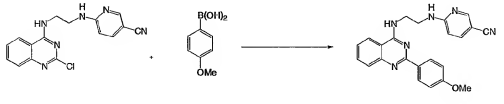
[00129] ^{1}H NMR (500 MHz, d_6-DMSO, ppm) δ8.60-8.55 (m, 1H), 8.39 (s, 1H), 8.26 (d, 1H), 7.84-7.78 (m, 2H), 7.76 (d, 1H), 7.71-7.69 (m, 1H), 7.65-7.52 (m, 3H), 7.50-7.42 (m, 2H), 6.61-6.46 (m, 1H), 3.77-3.59 (m, 4H); LC-MS (ES+) m/e= 401.03 (M+H); R_t= 1.89 min.

[00130] Example 8 **6-{2-[2-(2,4-Dimethoxy-phenyl)-quinazolin-4-ylamino]-ethylamino}-nicotinonitrile** (Compound I-185)



[00131] A mixture of 6-[2-(2-Chloro-quinazolin-4-ylamino)-ethylamino]-nicotinonitrile (65mg, 0.2 mmol), 2,4-dimethoxyphenylboronic acid (55mg, 0.3 mmol), tetrakis(triphenylphosphine)palladium (2mg) and aqueous saturated $NaHCO_3$ (0.5 ml) in 1,2-dimethoxyethane (3 ml) was stirred at 110°C under nitrogen for 14 h. The reaction mixture was concentrated. The residue was dissolved in a mixture of DMSO and MeOH and purified by reverse-phase HPLC. The title compound was obtained as a white solid (76 mg, 69%). ^{1}H NMR (500 MHz, DMSO(d_6)): δ13.20 (s, 1H), 10.20 (m, 1H), 8.38 (d, 2H), 8.00 (m, 2H), 7.82 (m, 1H), 7.78 (d, 2H), 7.72 (t, 1H), 6.80 (s, 1H), 6.70 (d, 1H), 3.90 (m, 7H), 3.83 (s, 3H). FIA-MS: (ES-) m/e= 425.3 (M-H), (ES+) m/e= 427.2 (M+H).

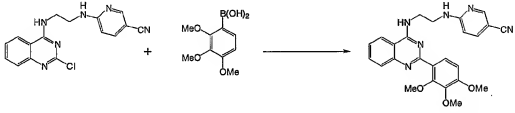
[00132] Example 9 **6-{2-[2-(4-Methoxy-phenyl)-quinazolin-4-ylamino]-ethylamino}-nicotinonitrile** (compound I-3)



[00133] This compound was prepared in an analogous manner as described in Example 8 using 4-methoxyphenylboronic acid. Purification was achieved on silica gel, eluting with 40-50% EtOAc in hexanes to give the tit le compound as a white solid (18.5mg, 30%).

[00134] ^{1}H NMR (500 MHz, d_6-DMSO, ppm) δ8.57-8.33 (m, 5H), 8.18 (d, 1H), 7.92-7.78 (m, 1H), 7.77-7.58 (m, 3H), 7.51-7.37 (m, 1H), 7.01 (d, 2H), 6.59-6.40 (m, 1H), 3.90-3.80 (m, 5H), 3.75-3.62 (m, 2H). LC-MS (ES+) m/e= 397.06 (M+H), (ES-) 395.11 (M-H); R_t= 2.10 min.

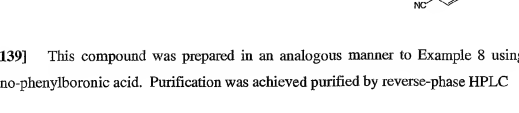
[00135] Example 10 **6-{2-[2-(2,3,4-Trimethoxy-phenyl)-quinazolin-4-ylamino]-ethylamino}-nicotinonitrile** (Compound I-186)



[00136] This compound was prepared in an analogous manner to described in Example 8 using 2,3,4-trimethoxyphenyl boronic acid. Purification was achieved on silica gel, eluting with 50-60% EtOAc in hexanes to give the title compound as a white solid (13mg, 18%).

[00137] ^{1}H NMR (500 MHz, d_6-DMSO, ppm) δ 8.39 (br s, 2H), 8.29-8.16 (m, 1H), 7.87-7.65 (m, 3H), 7.64-7.55 (m, 1H), 7.54-7.45 (m, 1H), 7.39 (d, 1H), 6.87 (d, 1H), 6.61-6.39 (br, 1H), 3.85 (d, 6H), 3.78 (s, 5H), 3.69-3.56 (m, 2H). LC-MS (ES+) m/e= 457.3 (M+H); R_t= 2.36 min.

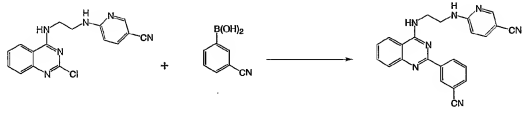
[00138] Example 11 **6-{2-[2-(2-Cyano-phenyl)-quinazolin-4-ylamino]-ethylamino}-nicotinonitrile** (Compound I-187)



[00139] This compound was prepared in an analogous manner to Example 8 using 2-cyano-phenylboronic acid. Purification was achieved purified by reverse-phase HPLC

[00140] ^{1}H NMR (500 MHz, DMSO(d_6)): δ9.7 (m, 1H), 8.38 (d, 2H), 8.00 (m, 2H), 7.82 (m, 1H), 7.78 (d, 2H), 7.72 (t, 1H), 6.80 (s, 1H), 6.70 (d, 1H), 4.04 (m, 2H), 3.65 (m, 2H). FIA-MS: (ES+) m/e= 392.3 (M+H).

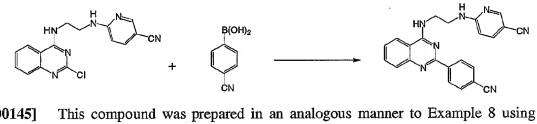
[00141] Example 12 **6-{2-[2-(3-Cyano-phenyl)-quinazolin-4-ylamino]-ethylamino}-nicotinonitrile** (compound I-29)



[00142] This compound was prepared in an analogous manner to Example 8 using 3-cyano-phenylboronic acid. Purification was achieved purified by reverse-phase HPLC

[00143] ^{1}H NMR (500 MHz, DMSO(d_6)): δ10.02 (m, 1H), 8.65 (s, 1H), 8.50 (d, 1H), 8.42 (m, 2H), 8.19 (d, 1H), 8.05 (t, 1H), 7.95 (d, 1H), 7.80 (m, 2H), 7.77 (t, 1H), 7.50 (br.s, 1H), 6.40 (br.s, 1H), 4.05 (m, 2H), 3.75 (m, 2H). FIA-MS: (ES+) m/e= 392.3 (M+H), (ES-) m/e= 504.1 (M + TFA).

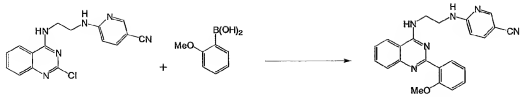
[00144] Example 13 **6-{2-[2-(4-Cyano-phenyl)-quinazolin-4-ylamino]-ethylamino}-nicotinonitrile** (compound I-19)



[00145] This compound was prepared in an analogous manner to Example 8 using 4-cyano-phenylboronic acid. Purification was achieved purified by reverse-phase HPLC

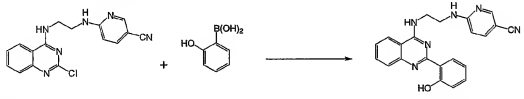
[00146] ^{1}H NMR (500 MHz, DMSO(d_6)): δ9.7 (m, 1H), 8.38 (m, 4H), 8.05 (d, 2H), 7.95 (t, 1H), 7.87 (d, 1H), 7.80 (m, 1H), 7.70 (m, 1H), 7.50 (m, 1H), 6.40 (m, 1H), 4.00 (m, 2H), 3.75 (m, 2H). FIA-MS: (ES+) m/e= 392.2 (M+H), (ES-) m/e= 504.1 (M + TFA).

[00147] Example 14 **6-{2-[2-(2-Methoxy-phenyl)-quinazolin-4-ylamino]-ethylamino}-nicotinonitrile** (Compound I-188)



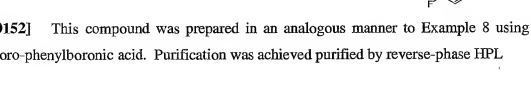
[00148] This compound was prepared in an analogous manner to Example 8 using 2-methoxy-phenylboronic acid. Purification was achieved purified by reverse-phase HPLC ^{1}H NMR (500 MHz, DMSO(d_6)): δ 13.80 (s, 1H), 10.30 (t, 1H), 8.48 (d, 1H), 8.32 (s, 1H), 8.06 (t, 1H), 7.93 (d, 1H), 7.76 (m, 2H), 7.68 (m, 2H), 7.50 (d, 1H), 7.29 (d, 1H), 7.10 (t, 1H), 6.40 (br.s, 1H), 4.05 (m, 2H), 4.00 (s, 3H), 3.75 (m, 2H). FIA-MS: (ES+) m/e= 397.3 (M+H), (ES-) m/e= 395.2 (M-H).

[00149] Example 15 **6-{2-[2-(2-Hydroxy-phenyl)-quinazolin-4-ylamino]-ethylamino}-nicotinonitrile** (Compound I-189)



[00150] This compound was prepared in an analogous manner to Example 8 using 2-hydroxy-phenylboronic acid. Purification was achieved purified by reverse-phase HPLC ^{1}H NMR (500 MHz, DMSO(d_6)): δ14.80 (s, 1H), 8.85 (t, 1H), 8.48 (s, 1H), 8.35 (d, 1H), 8.27 (d, 1H), 7.85 (m, 2H), 7.80 (d, 1H), 7.67 (m, 1H), 7.60 (t, 1H), 7.36 (t, 1H), 6.92 (m, 2H), 6.58 (m, 1H), 3.90 (m, 2H), 3.73 (m, 2H). FIA-MS: (ES+) m/e= 383.2 (M+H), (ES-) m/e= 381.2 (M-H).

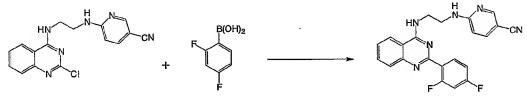
[00151] Example 16 **6-{2-[2-(2-Fluoro-phenyl)-quinazolin-4-ylamino]-ethylamino}-nicotinonitrile** (Compound I-190)



[00152] This compound was prepared in an analogous manner to Example 8 using 2-fluoro-phenylboronic acid. Purification was achieved purified by reverse-phase HPL

[00153] ^{1}H NMR (500 MHz, DMSO(d_6)): δ10.40 (s, 1H), 8.47 (d, 1H), 8.33 (s, 1H), 8.10 (t, 1H), 7.94 (d, 1H), 7.80 (m, 4H), 7.50 (m, 2H), 7.42 (t, 1H), 6.50 (m, 1H), 4.00 (m, 2H), 3.73 (m, 2H). FIA-MS: (ES+) m/e= 385.2 (M+H), (ES-) m/e= 383.2 (M-H).

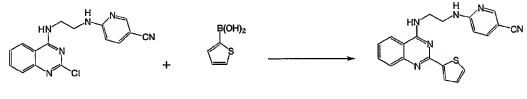
[00154] Example 17 **6-{2-[2-(2,4-Difluoro-phenyl)-quinazolin-4-ylamino]-ethylamino}-nicotinonitrile** (Compound I-191)



[00155] This compound was prepared in an analogous manner to Example 8 using 2,4-difluoro-phenylboronic acid. Purification was achieved purified by reverse-phase HPLC

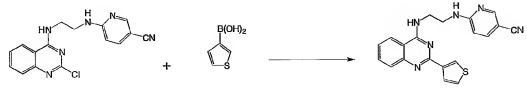
[00156] ^{1}H NMR (500 MHz, DMSO(d_6)): δ10.30 (s, 1H), 8.43 (d, 1H), 8.30 (s, 1H), 8.10 (t, 1H), 7.90 (m, 2H), 7.75 (m, 2H), 7.55 (td, 1H), 7.48 (m, 1H), 7.33 (td, 1H), 6.45 (m, 1H), 4.00 (m, 2H), 3.71 (m, 2H). FIA-MS: (ES+) m/e= 403.2 (M+H), (ES-) m/e= 515.1 (M+TFA).

[00157] Example 18 **6-[2-(2-Thiophen-2-yl-quinazolin-4-ylamino)-ethylamino]-nicotinonitrile** (Compound I-192)



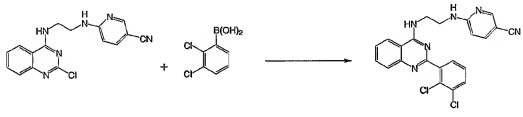
[00158] ^{1}H NMR (500 MHz, DMSO(d_6)): δ10.18 (s, 1H), 8.45 (m, 2H), 8.10 (d, 1H), 8.10 (t, 1H), 8.05 (t, 1H), 7.90 (d, 1H), 7.88 (br.s, 1H), 7.72 (t, 1H), 7.71 (br.s, 1H), 7.37 (d, 1H), 6.50 (br.s, 1H), 4.00 (m, 2H), 3.75 (m, 2H). FIA-MS: (ES+) m/e= 373.2 (M+H), (ES-) m/e= 485.1 (M+TFA).

[00159] Example 19 **6-[2-(2-Thiophen-3-yl-quinazolin-4-ylamino)-ethylamino]-nicotinonitrile** (compound I-32)



[00160] ^{1}H NMR (500 MHz, DMSO(d_6)): δ10.17 (s, 1H), 8.73 (s, 1H), 8.40 (m, 2H), 8.05 (t, 1H), 7.93 (d, 1H), 7.85 (m, 2H), 7.80 (d, 1H), 7.70 (t, 1H), 7.58 (br.s, 1H), 6.50 (br.s, 1H), 4.07 (m, 2H), 3.75 (m, 2H). FIA-MS: (ES+) m/e= 373.2 (M+H), (ES-) m/e= 485.1 (M+TFA).

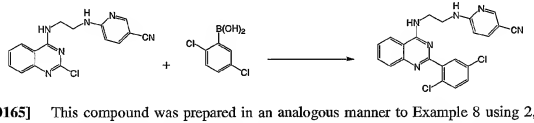
[00161] Example 20 **6-{2-[2-(2,3-Dichloro-phenyl)-quinazolin-4-ylamino]-ethylamino}-nicotinonitrile** (Compound I-193)



[00162] This compound was prepared in an analogous manner to Example 8 using 2,3-dichloro-phenylboronic acid. Purification was achieved purified by reverse-phase HPLC.

[00163] ^{1}H NMR (500 MHz, DMSO(d_6)): δ10.37 (s, 1H), 8.48 (s, 1H), 8.30 (d, 1H), 8.08 (t, 1H), 7.97 (d, 1H), 7.80 (m, 2H), 7.78 (m, 1H), 7.70 (d, 1H), 7.58 (t, 1H), 7.50 (dd, 1H), 6.43 (br.s, 1H), 3.97 (m, 2H), 3.68 (m, 2H). FIA-MS: (ES+) m/e= 435.0 (M+H), (ES-) m/e= 547.0 (M+TFA).

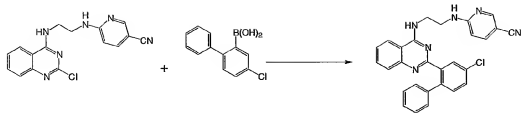
[00164] Example 21 **6-{2-[2-(2,5-Dichloro-phenyl)-quinazolin-4-ylamino]-ethylamino}-nicotinonitrile** (Compound I-194)



[00165] This compound was prepared in an analogous manner to Example 8 using 2,5-dichloro-phenylboronic acid. Purification was achieved purified by reverse-phase HPLC.

[00166] ^{1}H NMR (500 MHz, DMSO(d_6)): δ10.35 (s, 1H), 8.52 (d, 1H), 8.30 (d, 1H), 8.10 (t, 1H), 7.97 (d, 1H), 7.82 (m, 3H), 7.78 (m, 1H), 7.70 (s, 1H), 7.48 (d, 1H), 6.43 (br.s, 1H), 3.92 (m, 2H), 3.60 (m, 2H). FIA-MS: (ES+) m/e= 435.0 (M+H), (ES-) m/e= 547.0 (M+TFA).

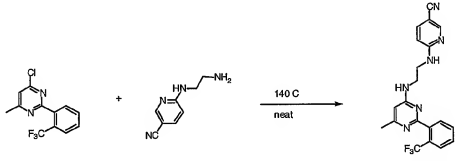
[00167] Example 22 **6-{2-[2-(4-Chloro-biphenyl-2-yl)-quinazolin-4-ylamino]-ethylamino}-nicotinonitrile** (Compound I-195)



[00168] This compound was prepared in an analogous manner to Example 8 using 4-chlorobiphenylboronic acid. Purification was achieved purified by reverse-phase HPL

[00169] ^{1}H NMR (500 MHz, DMSO(d_6)): δ10.20 (s, 1H), 8.39 (d, 1H), 8.30 (s, 1H), 8.05 (t, 1H), 7.85 (d, 1H), 7.78 (m, 3H), 7.70 (t, 1H), 7.65 (d, 1H), 7.55 (dd, 1H), 7.30 (m, 5H), 6.45 (d, 1H), 3.45 (m, 2H), 3.33 (m, 2H). FIA-MS: (ES+) m/e= 443.2 (M+H), (ES-) m/e= 441.2 (M-H), 477.2 (M+TFA).

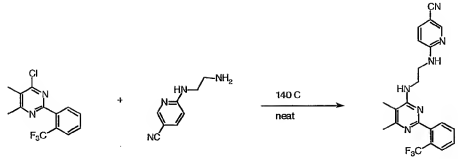
[00170] Example 23 **6-{2-[6-Methyl-2-(2-trifluoromethyl-phenyl)-pyrimidin-4-ylamino]-ethylamino}-nicotinonitrile** (Compound I-196)



[00171] This compound was prepared in an analogous manner as described in Example 1 using 4-chloro-6-methyl-2-(2-trifluoromethyl-phenyl)-pyrimidine. Purification was achieved by silica gel chromatography (1:1 ethyl acetate/ hexane, 3:1 ethyl acetate/hexane, 4:1 ethyl acetate/hexane, 6:1 ethyl acetate/hexane)to yield the title compound (50 mg, 69%).

[00172] ^{1}H NMR (500 MHz, d_6-DMSO, ppm) δ 2.25 (s, 3H), 3.4-3.52 (br m, 4H), 6.30 (br s, 1H), 6.50-6.56 (m, 1H), 7.50-7.60 (m, 1H), 7.62-7.68 (m, 3H), 7.69-7.77 (m, 2H), 7.80-7.82 (m, 1H), 8.40 (br s, 1H); LC-MS (ES+) m/e= 399.13 (M+H); R_t= 1.90 min.

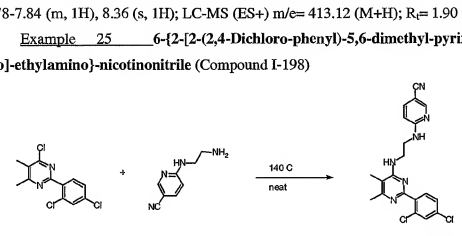
[00173] Example 24 **6-{2-[5,6-Dimethyl-2-(2-trifluoromethyl-phenyl)-pyrimidin-4-ylamino]-ethylamino}-nicotinonitrile** (Compound I-197)



[00174] This compound was prepared in an analogous manner as described in Example 1 using 4-chloro-5,6-dimethyl-2-(2-trifluoromethyl-phenyl)-pyrimidine. Purification was achieved by silica gel chromatography (1:1 ethyl acetate/ hexane, 2:1 ethyl acetate/hexane) to yield the title compound (43 mg, 60%).

[00175] ^{1}H NMR (500 MHz, d_6-DMSO, ppm) δ2.25s, 3H), 2.30 (s, 3H), 3.45-3.59 (m, 4H), 6.50 (br s, 1H), 6.94 (br s, 1H), 7.52-7.60 (m, 1H), 7.60-7.66 (m, 2H), 7.69-7.75 (m, 2H), 7.78-7.84 (m, 1H), 8.36 (s, 1H); LC-MS (ES+) m/e= 413.12 (M+H); R_t= 1.90 min.

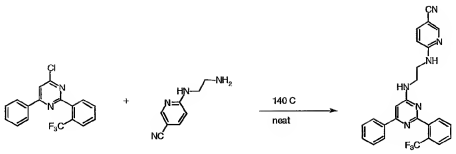
[00176] Example 25 **6-{2-[2-(2,4-Dichloro-phenyl)-5,6-dimethyl-pyrimidin-4-ylamino]-ethylamino}-nicotinonitrile** (Compound I-198)



[00177] This compound was prepared in an analogous manner as described in Example 1 using 4-chloro-2-(2,4-dichloro-phenyl)-5,6-dimethyl-pyrimidine. Purification was achieved by silica gel chromatography (1:1 ethyl acetate/ hexane, 2:1 ethyl acetate/hexane) to yield the title compound (31 mg, 43%).

[00178] ^{1}H NMR (500 MHz, d_6-DMSO, ppm) δ 2.02 (s, 3H), 2.30 (s, 3H), 3.48-3.56 (m, 4H), 6.50 (br s, 1H), 7.00 (br s, 1H), 7.47 (d, 1H), 7.55-7.60 (m, 1H), 7.61-7.69 (m, 2H), 7.70-7.75 (m, 1H), 8.35 (s, 1H); LC-MS (ES+) m/e= 413.00 (M+H); R_t= 1.95 min.

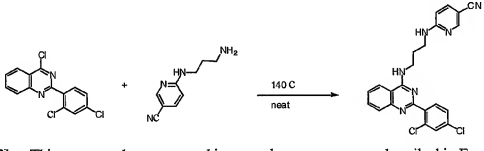
[00179] Example 26 **6-{2-[6-Phenyl-2-(2-trifluoromethyl-phenyl)-pyrimidin-4-ylamino]-ethylamino}-nicotinonitrile** (Compound I-199)



[00180] This compound was prepared in an analogous manner as described in Example 1 using 4-chloro-6-phenyl-2-(2-trifluoromethyl-phenyl)-pyrimidine. Purification was achieved by silica gel chromatography (1:1 ethyl acetate/ hexane, 2:1 ethyl acetate/hexane) to yield the title compound (48 mg, 70%).

[00181] ^{1}H NMR (500 MHz, d_6-DMSO, ppm) δ 3.45 (m, 4H), 6.50-6.58 (m, 1H), 6.92-7.00 (m, 1H), 7.44-7.52 (m, 3H), 7.55-7.62 (m, 1H), 7.65-7.70 (m, 1H), 7.70-7.80 (m, 4H), 7.82-7.87 (m, 1H), 7.98-8.05 (m, 2H), 8.35-8.42 (m, 1H); LC-MS (ES+) m/e= 461.07 (M+H); R_t= 3.33 min.

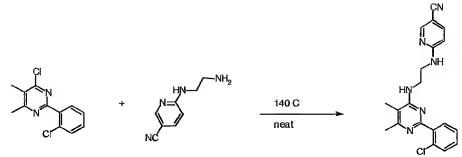
[00182] Example 27 **6-{3-[2-(2,4-Dichloro-phenyl)-quinazolin-4-ylamino]-propylamino}-nicotinonitrile** (Compound I-97)



[00183] This compound was prepared in an analogous manner as described in Example 1 using 4-chloro-2-(2,4-dichloro-phenyl)-quinazoline and 6-(3-amino-propylamino)-nicotinonitrile, (which was prepared in a similar fashion to 6-(2-amino-ethylamino)-nicotinonitrile). Purification was achieved by silica gel chromatography (1:1 ethyl acetate/ hexane, 2:1 ethyl acetate/hexane) to yield the title compound (50 mg, 57%).

[00184] ^{1}H NMR (500 MHz, d_6-DMSO, ppm) δ 1.91-2.0 (m, 2H), 3.37-3.45 (m, 2H), 3.60-3.70 (m, 2H), 6.47 (d, 1H), 7.50-7.54 (m, 1H), 7.54-7.60 (m, 1H), 7.60-7.65 (m, 2H), 7.68-7.70 (m, 1H), 7.72-7.85 (m, 3H), 8.28 (d, 1H), 8.35 (s, 1H), 8.42-8.52 (m, 1H); LC-MS (ES+) m/e= 448.94 (M+H); R_t= 2.31 min.

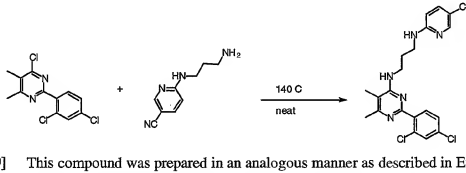
[00185] Example 28 **6-{2-[2-(2-Chloro-phenyl)-5,6-dimethyl-pyrimidin-4-ylamino]-ethylamino}-nicotinonitrile** (Compound I-143)



[00186] This compound was prepared in an analogous manner as described in Example 1 using 4-chloro-2-(2-chloro-phenyl)-5,6-dimethyl-pyrimidine. Purification was achieved by silica gel chromatography (2:1 ethyl acetate/ hexane, 4:1 ethyl acetate/hexane) to yield the title compound (46 mg, 61%).

[00187] ^{1}H NMR (500 MHz, d_6-DMSO, ppm) δ2.02 (s, 3H), 2.31 (s, 3H), 3.46-3.65 (m, 4H), 6.47-6.60 (m, 1H), 6.92-7.04 (m, 1H), 7.36-7.45 (m, 2H), 7.48-7.52 (m, 1H), 7.54-7.68 (m, 2H), 7.70-7.80 (m, 1H), 8.34-8.42 (m, 1H); LC-MS (ES+) m/e= 379.02 (M+H); R_t= 1.72 min.

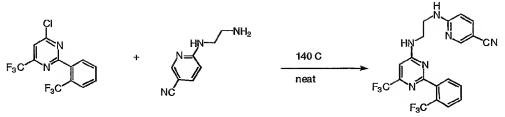
[00188] Example 29 **6-{3-[2-(2,4-Dichloro-phenyl)-5,6-dimethyl-pyrimidin-4-ylamino]-propylamino}-nicotinonitrile** (Compound I-142)



[00189] This compound was prepared in an analogous manner as described in Example 1 using 4-chloro-2-(2,4-dichloro-phenyl)-5,6-dimethyl-pyrimidine and 6-(3-amino-propylamino)-nicotinonitrile, (which was prepared in a similar fashion to 6-(2-amino-ethylamino)-nicotinonitrile). Purification was achieved by silica gel chromatography (1:1 ethyl acetate/ hexane, 2:1 ethyl acetate/hexane) to yield the title compound (32 mg, 43%).

[00190] ^{1}H NMR (500 MHz, d_6-DMSO, ppm) δ1.79-1.86 (m, 2H), 2.01 (s, 3H), 2.30 (s, 3H), 3.30-3.40 (m, 2H), 3.41-3.50 (m, 2H), 6.46 (d, 1H), 6.83-6.92 (m, 1H), 7.42-7.50 (m, 1H), 7.56-7.70 (m, 4H), 8.31 (s, 1H); LC-MS (ES+) m/e= 426.98 (M+H); R_t= 2.07 min.

[00191] Example 30 **6-{2-[6-Trifluoromethyl-2-(2-trifluoromethyl-phenyl)-pyrimidin-4-ylamino]-ethylamino}-nicotinonitrile** (Compound I-202)

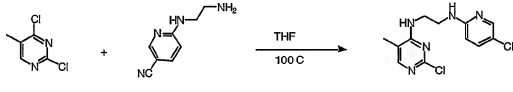


[00192] This compound was prepared in an analogous manner as described in Example 1 using 4-chloro-6-trifluoromethyl-2-(2-trifluoromethyl-phenyl)-pyrimidine. Purification was achieved by silica gel chromatography (1:1 ethyl acetate/ hexane, 3:1 ethyl acetate/hexane) to yield the title compound (18 mg, 26%).

[00193] ^{1}H NMR (500 MHz, d_6-DMSO, ppm) δ3.46-3.55 (m, 2H), 3.56-3.64 (m, 2H), 6.47-6.53 (m, 1H), 6.88 (s, 1H), 7.58 (d, 1H), 7.66-7.81 (m, 4H), 7.82-7.90 (m, 1H), 8.32-8.41 (m, 2H); LC-MS (ES+) m/e= 453.04 (M+H); R_t= 3.86 min.

[00194] Example 31 **6-{2-[2-(4-Chloro-phenyl)-5-methyl-pyrimidin-4-ylamino]-ethylamino}-nicotinonitrile** (Compound I-158)

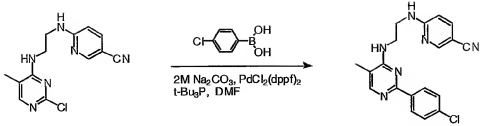
[00195] Step A. 6-[2-(2-Chloro-5-methyl-pyrimidin-4-ylamino)-ethylamino]-nicotinonitrile



[00196] A mixture of 2,4-Dichloro-5-methyl-pyrimidine 250 mg, 1.53 mmol) and 6-(2-amino-ethylamino)-nicotinonitrile (373 mg, 2.30 mmol, prepared according to the method described by Nuss *et al*, WO 99/65997) was dissolved in tetrahydrofuran (10 mL). The reaction mixture was heated at 100 C for 2 days. Purification was achieved by silica gel chromatography (1:3 hexane/ethyl acetate, 1:4 hexane/ethyl acetate, 1:6 hexane/ethyl acetate) to yield the title compound as a white solid (154 mg, 35%).

[00197] ^{1}H NMR (500 MHz, d_6-DMSO, ppm) δ1.94 (s, 3H), 3.45-3.61 (m, 4H), 6.48-6.68 (m, 1H), 7.40-7.45 (m, 1H), 7.61-7.78 (m, 2H), 7.80 (s, 1H), 8.40 (s, 1H); LC-MS (ES+) m/e= 288.98 (M+H); R_t= 2.09 min.

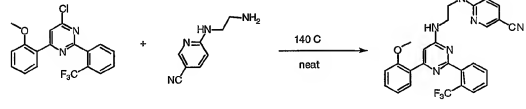
[00198] Step B. 6-{2-[2-(4-Chloro-phenyl)-5-methyl-pyrimidin-4-ylamino]-ethylamino}-nicotinonitrile



[00199] 6-[2-(2-Chloro-5-methyl-pyrimidin-4-ylamino)-ethylamino]-nicotinonitrile (50 mg, 0.174 mmol) was dissolved in N,N-dimethylformamide (2 mL) under an argon atmosphere. 4-chlorophenylboronic acid (41 mg, 0.260 mmol), 2M aqueous sodium carbonate (435 µL, 0.870 mmol), 1,1'-bis(diphenylphosphino)ferrocene-palladium (II) dichloride (8 mg, 0.01 mmol), and tri-t-butylphosphine (43 µL, 0.174 mmol) were added and the reaction mixture was heated at 80°C for 16 hours. The mixture was diluted with dichloromethane then washed with water (1x) and brine (1x). The organic layer was dried over magnesium sulfate and concentrated in vacuo. Purification was achieved by preparative HPLC (20% to 60% 0.1% trifluoroacetic acid in acetonitrile over 10 minutes) to yield the title compound as a white solid (10.2 mg, 16%).

[00200] ^{1}H NMR (500 MHz, d_6-DMSO, ppm) δ2.12 (s, 3H), 3.50-3.70 (m, 2H), 3.78-3.91 (m, 2H), 6.35-6.52 (m, 1H), 7.50-7.61 (m, 1H), 7.66 (d, 2H), 7.75-7.87 (m, 1H), 8.08 (d, 2H), 8.16 (s, 1H), 8.35-8.48 (m, 1H), 8.60-8.70 (m, 1H); LC-MS (ES+) m/e= 364.95 (M+H); R_t= 2.25 min.

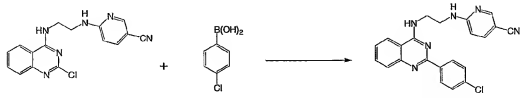
[00201] Example 32 **6-{2-[6-(2-Methoxy-phenyl)—2-(2-trifluoromethyl-phenyl)-pyrimidin-4-ylamino]-ethylamino}-nicotinonitrile** (Compound I-203)



[00202] This compound was prepared in an analogous manner as described in Example 1 using 4-chloro-6-(2-methoxy-phenyl)-2-(2-trifluoromethyl-phenyl)-pyrimidine. Purification was achieved by preparative HPLC (20% to 60% 0.1% trifluoroacetic acid in acetonitrile over 10 minutes) to yield the title compound (28.4 mg, 42%).

[00203] ^{1}H NMR (500 MHz, d_6-DMSO, ppm) δ3.45-3.65 (m, 4H), 3.87 (s, 3H), 6.50-6.55 (m, 1H), 7.02-7.14 (m, 2H), 7.18-7.25 (m, 1H), 7.48-7.65 (m, 2H), 7.72-7.97 (m, 6H), 8.32 (s, 1H); LC-MS (ES+) m/e= 491.18 (M+H); R_t= 2.56 min.

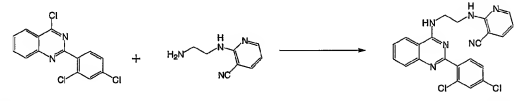
[00204] Example 33 **6-{2-[2-(2,4-Difluoro-phenyl)-quinazolin-4-ylamino]-ethylamino}-nicotinonitrile** (Compound I-2)



[00205] This compound was prepared in an analogous manner to Example 8 using 4-chloro-phenylboronic acid. Purification was achieved purified by reverse-phase HPL

[00206] ^{1}H NMR (500 MHz, DMSO(d_6)): δ8.52-8.37 (m, 2H), 8.32-8.20 (m, 2H), 8.30 (s, 1H),8.11-7.39 (m, 8H), 6.53-6.34 (m, 1H), 4.09-3.95 (m, 2H), 3.80-3.65 (m, 2H). LC-MS (ES+) m/e= 401.10 (M+H); R_t= 2.20 min

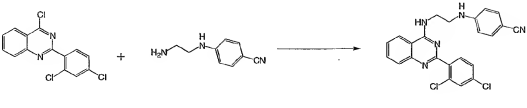
[00207] Example 34 **2-{2-[2-(2,4-Dichloro-phenyl)-quinazolin-4-ylamino]-ethylamino}-nicotinonitrile** (Compound I-65)



[00208] This compound was prepared in an analogous manner to Example 1 using 2-(2-amino-ethylamino)nicotinonitrile (prepared from 6-chloro pyridine-2-carbonitrile according to the method described by Nuss *et al*, WO 99/65997). Isolated as a white solid (3.0mg, 2%).

[00209] ^{1}H NMR (500 MHz, DMSO(d_6)): δ10.30-10.10 (1H, bs), 8.45 (1H, m), 8.17 (1H, m), 8.10-8.05 (1H, m), 7.90-7.70 (6H, m), 7.35 (1H, m), 6.55 (1H, m), 4.0-7.90 (2H, m), 3.80-3.70 (2H, m). HPLC Rt= 3.10 min,; FIA (M+H) 434.9, (M-H) 432.6,;

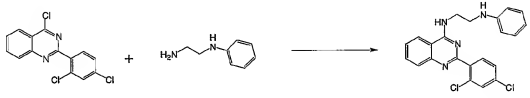
[00210] Example 35 **4-{2-[2-(2,4-Dichloro-phenyl)-quinazolin-4-ylamino]-ethylamino}-benzonitrile** (Compound I-62)



[00211] This compound was prepared in an analogous manner to Example 1 using 4-(2-amino-ethylamino)-benzonitrile (prepared from 4-fluorobenzonitrile according to the method described by Nuss *et al*, WO 99/65997). Isolated as a white solid (23.6mg, 28%.

[00212] ^{1}H NMR (500 MHz, DMSO-d_6: δ10.20-10.00 (1H, bs), 8.40 (1H, m), 8.00 (1H, m), 8.0-7.60 (6H, m), 7.20 (2H, m), 6.60 (2H, m), 3.80-3.70 (2H, m), 3.45-3.35 (2H, m. HPLC Rt = 3.23 min,; FIA (M+H) m/e= 434.0, (M-H) m/e= 431.7

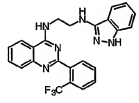
[00213] Example 36 ***N*-[2-(2,4-Dichloro-phenyl)-quinazolin-4-yl]-*N*'-phenyl-ethane-1,2-diamine** (Compound I-64)



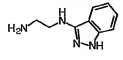
[00214] This compound was prepared in an analogous manner to Example 1 using N-phenylethylenediamine. Isolated as a white solid (49.9mg, 28%)

[00215] ^{1}H NMR (500 MHz, DMSO-d_6: δ10.40-10.25 (1H, bs), 8.45 (1H, m), 8.05 (1H, m), 7.92 (1H, s), 8.85-7.60 (4H, m), 6.90 (2H, m), 6.60 (2H, m), 6.45 (1H, m), 3.85-3.75 (2H, m), 3.40-3.30 (2H, m). HPLC Rt = 3.22 min; FIA (M+H) m/e= 409.0, (M-H) m/e= 407.0

[00216] Example 37 **N-(1H-Indazol-3-yl)-N'-[2-(2-trifluoromethyl-phenyl)-quinazolin-4-yl]-ethane-1,2-diamine, trifluoro-acetic acid salt** (Compound I-10)



[00217] **N1-(1H-Indazol-3-yl)-ethane-1,2-diamine**



[00218] A mixture of 3-aminoindazole (0.40 g, 3 mmol) and 2-bromoethylamine hydrobromide (0.62 g, 3 mmol) in ethanol (15 mL) was sealed in a pressure tube and heated at 160-170°C for 2 days. The crude mixture was partitioned between aqueous sodium

bicarbonate and 1:9 methanol:ethyl acetate. The organic layer was dried over sodium sulfate and the solvent was then evaporated. Purification by flash chromatography (SiO_2) eluted with 0.2:2:8 ammonium hydroxide:methanol:dichloromethane provided N1-(1H-indazol-3-yl)-ethane-1,2-diamine and 1-(2-aminoethyl)-1H-indazol-3-ylamine, both containing impurities.

[00219] N1-(1H-Indazol-3-yl)-ethane-1,2-diamine was isolated (52.5 mg, 10% yield, 74.7% purity by HPLC) as a colorless film. R_f=0.05 (SiO_2, 1:9 methanol: dichloromethane; ^{1}H-NMR (500 MHz, CD_3OD, ppm) δ 7.65 (d, J=7.3 Hz, 1H), 7.27 (m, 2H), 6.96 (dt, J=1.0, 7.2 Hz, 1H), 3.48 (t, J=6.5 Hz, 2H), 3.01 (t, J=6.0 Hz, 2H) (+ impurity peaks); MS (LC/MS) 177.01 (M+H); HPLC R_t=1.100 min.

[00220] 1-(2-Aminoethyl)-1H-indazol-3-ylamine was isolated (57.1 mg, 11% yield) as a colorless film. R_f=0.16 (SiO_2, 1:9 methanol:dichloromethane); ^{1}H-NMR (500 MHz, CD_3OD, ppm) δ 7.56 (d, J=7.4 Hz, 1H), 7.23 (d, J=8.8 Hz, 1H), 7.14 (t, J=7.6 Hz, 1H), 6.75 (t, J=7.5 Hz, 1H), 4.19 (t, J=6.3 Hz, 2H), 3.08 (t, J=6.3 Hz, 2H) (+ impurity peaks); MS (LC/MS) 177.01 (M+H); HPLC R_t= 0.500 min.

[00221] A mixture of 4-chloro-2-(2-trifluoromethyl-phenyl)-quinazoline (0.05 g, 0.16 mmol) and N1-(1H-indazol-3-yl)-ethane-1,2-diamine (0.03 g, 0.16 mmol) in dimethylformamide (2 mL) was heated at 120-125°C for 2 h. After cooling, the reaction mixture was poured into water (30 mL) and was treated with saturated bicarbonate (10 mL). The resulting precipitate was filtered off and was then washed with water. Purification by preparative HPLC (Gilson) provided the title compound (3% yield) as a yellow film.

[00222] ^{1}H-NMR (500 MHz, d_6-DMSO, ppm) δ 11.6 (s, 1H), 8.48 (d, J=7.8 Hz, 1H), 7.97 (m, 2H), 7.81 (m, 6H), 7.63 (d, J=8.0 Hz, 1H), 7.25 (d, J=2.5 Hz, 1H), 6.89 (m, 1H), 3.93 (t, J=5.8 Hz, 2H), 3.61 (t, J=6.1 Hz, 2H); MS (LC/MS) 449.14 (M+H); HPLC R_t= 2.677 min.

[00223] EXAMPLE 12 - BIOLOGICAL TESTING

[00224] The activity of the compounds as protein kinase inhibitors is assayed *in vitro, in vivo* or in a cell line. *In vitro* assays include assays that determine inhibition of either the phosphorylation activity or ATPase activity of the activated protein kinase. Alternate *in vitro* assays quantitate the ability of the inhibitor to bind to the protein kinase. Inhibitor binding may be measured by radiolabelling the inhibitor prior to binding, isolating the inhibitor/protein kinase complex and determining the amount of radiolabel bound.

Alternatively, inhibitor binding may be determined by running a competition experiment where new inhibitors are incubated with the protein kinase bound to known radioligands.

[00225] K_i DETERMINATION FOR THE INHIBITION OF GSK-3

[00226] Compounds were screened for their ability to inhibit GSK-3β (AA 1-420) activity using a standard coupled enzyme system [Fox et al. *Protein Sci.* 7, 2249 (1998)]. Reactions were carried out in a solution containing 100 mM HEPES (pH 7.5), 10 mM $MgCl_2$, 25 mM NaCl, 300 μM NADH, 1 mM DTT and 1.5% DMSO. Final substrate concentrations in the assay were 20 μM ATP (Sigma Chemicals, St Louis, MO) and 300 μM peptide (American Peptide, Sunnyvale, CA). Reactions were carried out at 30 °C and 20 nM GSK-3β. Final concentrations of the components of the coupled enzyme system were 2.5 mM phosphoenolpyruvate, 300 μM NADH, 30 μg/ml pyruvate kinase and 10 μg/ml lactate dehydrogenase.

[00227] An assay stock buffer solution was prepared containing all of the reagents listed above with the exception of ATP and the test compound of interest. The assay stock buffer solution (175 μl) was incubated in a 96 well plate with 5 μl of the test compound of interest at final concentrations spanning 0.002 μM to 30 μM at 30 °C for 10 min. Typically, a 12 point titration was conducted by preparing serial dilutions (from 10 mM compound stocks) with DMSO of the test compounds in daughter plates. The reaction was initiated by the addition of 20 μl of ATP (final concentration 20 μM). Rates of reaction were obtained using a Molecular Devices Spectramax plate reader (Sunnyvale, CA) over 10 min at 30 °C. The K_i values were determined from the rate data as a function of inhibitor concentration.

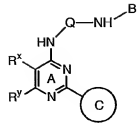
[00228] The following compounds were shown to have K_i values less than 0.1 μM for GSK-3: compounds **I-1, I-2, I-8, I-9, I-11, I-19, I-62, I-118, I-183, I-188, I-189, I-190, I-191, I-195, I-197, I-198,** and **I-200**.

[00229] The following compounds were shown to have K_i values between 0.1 and 1.0 μM for GSK-3: compounds **I-3, I-10, I-29, I-32, I-105, I-113, I-158, I-182, I-187, I-192, I-193, I-194, I-196, I-199, I-202,** and **I-203**.

[00230] While we have hereinbefore presented a number of embodiments of this invention, it is apparent that our basic construction can be altered to provide other embodiments that utilize the compounds and methods of this invention. Therefore, it will be appreciated that the scope of this invention is to be defined by the appended claims rather than by the specific embodiments that have been represented by way of example.

CLAIMS

1. A compound of formula **I**:



I

or a pharmaceutically acceptable derivative or prodrug thereof, wherein:

B is an optionally substituted 5-6 membered monocyclic or 8-10 membered bicyclic aromatic ring, wherein said monocyclic or bicyclic ring has 0-4 heteroatoms selected from oxygen, sulfur or nitrogen;

Q is a C_{1-4} alkylidene chain, wherein each methylene unit of said Q is substituted by R^2 and $R^{2'}$, and up to two non-adjacent methylene units of said Q are optionally and independently replaced by $-SO_2$ or -C(=O);

Ring C is selected from a phenyl, thienyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, or 1,2,4-triazinyl ring, wherein said Ring C optionally has one or two ortho substituents independently selected from $-R^1$, any substitutable carbon position on Ring C is independently substituted by $-R^5$, or two adjacent substituents on Ring C are optionally taken together with their intervening atoms to form a fused, unsaturated or partially unsaturated, 5-6 membered ring having 0-3 heteroatoms selected from oxygen, sulfur or nitrogen, said fused ring being optionally substituted by halo, oxo, or $-R^8$;

R^1 is selected from –halo, -CN, $-NO_2$, T-V-R^6, phenyl, 5-6 membered heteroaryl ring, 5-6 membered heterocyclyl ring, or C_{1-6} aliphatic group, said phenyl, heteroaryl, and heterocyclyl rings each optionally substituted by up to three groups independently selected from halo, oxo, or $-R^8$, said C_{1-6} aliphatic group optionally substituted with halo, cyano, nitro, or oxygen, or R^1 and an adjacent substituent taken together with their intervening atoms form said ring fused to Ring C;

each R^2 is independently selected from H, -OH, C_{1-10} aliphatic; (C_{1-10} aliphatic)-NH-(C_{1-10} aliphatic); -O-(C_{1-10} aliphatic); $-NH_2$, -NH(C_{1-10} aliphatic), -N(C_{1-10} aliphatic)$_2$, -C(=O)R, aryl, or heteroaryl, wherein said aliphatic, aryl, or heteroaryl is optionally substituted;

R is selected from an optionally substituted group selected from C_{1-10} aliphatic, aryl, aralkyl, heteroaryl, or heteroaralkyl;

each $R^{2'}$ is independently selected from H or an optionally substituted C_{1-10} aliphatic group;

R^X and R^Y are independently selected from T-R^3, or R^X and R^Y are taken together with their intervening atoms to form a fused, partially saturated or aromatic, 5-8 membered ring having 0-3 ring heteroatoms selected from oxygen, sulfur, or nitrogen, wherein any substitutable carbon on said fused ring formed by R^X and R^Y is substituted by oxo or T-R^3, and any substitutable nitrogen on said ring formed by R^X and R^Y is substituted by R^4;

T is a valence bond or a C_{1-4} alkylidene chain;

R^3 is selected from –R', -halo, -OR', -C(=O)R', $-CO_2R'$, -COCOR', $-COCH_2COR'$, $-NO_2$, -CN, -S(O)R', $-S(O)_2R'$, -SR', $-N(R^4)_2$, $-CON(R^7)_2$, $-SO_2N(R^7)_2$, -OC(=O)R', $-N(R^7)COR'$, $-N(R^7)CO_2$(optionally substituted C_{1-6} aliphatic), $-N(R^4)N(R^4)_2$, $-C{=}NN(R^4)_2$, -C=N-OR', $-N(R^7)CON(R^7)_2$, $-N(R^7)SO_2N(R^7)_2$, $-N(R^4)SO_2R$, or $-OC(=O)N(R^7)_2$;

each R' is independently selected from hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, C_{6-10} aryl, a heteroaryl ring having 5-10 ring atoms, or a heterocyclyl ring having 5-10 ring atoms;

each R^4 is independently selected from –R^7, -COR^7, $-CO_2$(C_{1-6} aliphatic), $-CON(R^7)_2$, or $-SO_2R^7$, or two R^4 on the same nitrogen are taken together to form a 5-8 membered heterocyclyl or heteroaryl ring;

each R^5 is independently selected from –R', halo, -OR', -C(=O)R', $-CO_2R'$, -COCOR', $-NO_2$, -CN, -S(O)R', $-SO_2R'$, -SR', $-N(R^4)_2$, $-CON(R^4)_2$, $-SO_2N(R^4)_2$, -OC(=O)R', $-N(R^4)COR'$, $-N(R^4)CO_2$(optionally substituted C_{1-6} aliphatic), $-N(R^4)N(R^4)_2$, $-C{=}NN(R^4)_2$, -C=N-OR', $-N(R^4)CON(R^4)_2$, $-N(R^4)SO_2N(R^4)_2$, $-N(R^4)SO_2R'$, or $-OC(=O)N(R^4)_2$, or R^5 and an adjacent substituent taken together with their intervening atoms form said ring fused to Ring C;

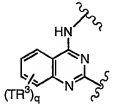
V is –O-, -S-, -SO-, $-SO_2$-, $-N(R^6)SO_2$-, $-SO_2N(R^6)$-, $-N(R^6)$-, -CO-, $-CO_2$-, $-N(R^6)CO$-, $-N(R^6)C(O)O$-, $-N(R^6)CON(R^6)$-, $-N(R^6)SO_2N(R^6)$-, $-N(R^6)N(R^6)$-, $-C(O)N(R^6)$-, $-OC(O)N(R^6)$-, $-C(R^6)_2O$-, $-C(R^6)_2S$-, $-C(R^6)_2SO$-, $-C(R^6)_2SO_2$-, $-C(R^6)_2SO_2N(R^6)$-, $-C(R^6)_2N(R^6)$-, $-C(R^6)_2N(R^6)C(O)$-, $-C(R^6)_2N(R^6)C(O)O$-, $-C(R^6){=}NN(R^6)$-, $-C(R^6){=}N-O$-, $-C(R^6)_2N(R^6)N(R^6)$-, $-C(R^6)_2N(R^6)SO_2N(R^6)$-, or $-C(R^6)_2N(R^6)CON(R^6)$-;

each R^6 is independently selected from hydrogen or an optionally substituted C_{1-4} aliphatic group, or two R^6 groups on the same nitrogen atom are taken together with the nitrogen atom to form a 5-6 membered heterocyclyl or heteroaryl ring;

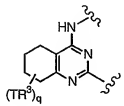
each R^7 is independently selected from hydrogen or an optionally substituted C_{1-6} aliphatic group, or two R^7 on the same nitrogen are taken together with the nitrogen to form a 5-8 membered heterocyclyl or heteroaryl ring; and

each R^8 is independently selected from an optionally substituted C_{1-4} aliphatic group, $-OR^6$, $-SR^6$, $-COR^6$, $-SO_2R^6$, $-N(R^6)_2$, $-N(R^6)N(R^6)_2$, $-CN$, $-NO_2$, $-CON(R^6)_2$, or $-CO_2R^6$.

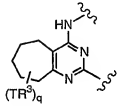
2. The compound according to claim 1, wherein ring A is selected from one of:



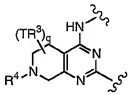
I-A



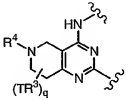
I-B



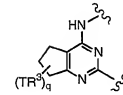
I-C



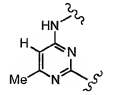
I-D



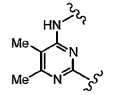
I-E



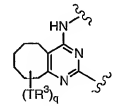
I-F



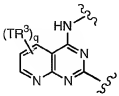
I-G

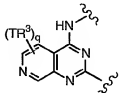


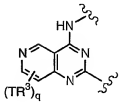
I-H



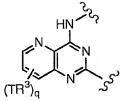
I-I



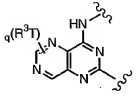




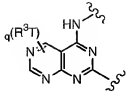
I-J



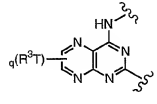
I-K



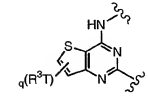
I-L



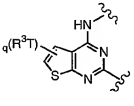
I-M



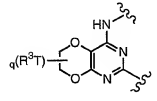
I-N



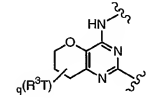
I-O



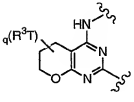
I-P



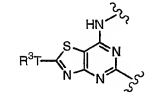
I-Q



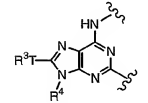
I-R



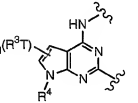
I-S



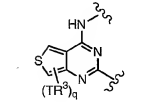
I-T



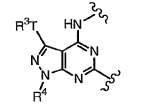
I-U



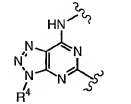
I-V



I-W



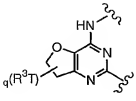
I-X



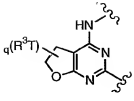
I-Y

I-Z

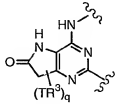
I-AA



I-BB



I-CC



I-DD

3. The compound of claim 2, wherein Ring A is selected from one of **I-A**, **I-B**, **I-C**, **I-D**, **I-E**, **I-F**, **I-G**, **I-H**, **I-I**, **I-J**, **I-K**, **I-L**, or **I-M**.

4. The compound of claim 2, wherein Ring A is selected from one of **I-A**, **I-B**, **I-C**, **I-F**, or **I-H**.

5. The compound of claim 2, wherein q is 0-4, and T-R^3 substituents are selected from –R', halo, -OR', -C(=O)R', -CO_2R', -COCOR', -NO_2, -CN, -S(O)R', -SO_2R', -SR', -N(R^4)$_2$, -CON(R^4)$_2$, -SO_2N(R^4)$_2$, -OC(=O)R', -N(R^4)COR', -N(R^4)CO_2(optionally substituted C_{1-6} aliphatic), -N(R^4)N(R^4)$_2$, -C=NN(R^4)$_2$, -C=N-OR', -N(R^4)CON(R^4)$_2$, -N(R^4)SO_2N(R^4)$_2$, -N(R^4)SO_2R', or -OC(=O)N(R^4)$_2$. Exemplary R^4 substituents include –R^7, -COR^7, -CO_2(C_{1-6} aliphatic), -CON(R^7)$_2$, or -SO_2R^7, or two R^4 on the same nitrogen are taken together to form a 5-8 membered heterocyclyl or heteroaryl ring.

6. The compound of claim 1, wherein compounds of formula **I** have a monocyclic pyrimidine ring system which is substituted by R^X and R^Y, wherein R^X groups include hydrogen, alkyl- or dialkylamino, acetamido, or a C_{1-4} aliphatic group such as methyl, ethyl, cyclopropyl, isopropyl or t-butyl, and R^Y groups include T-R^3 wherein T is a valence bond or a methylene, and R^3 is –R', -N(R^4)$_2$, or –OR'.

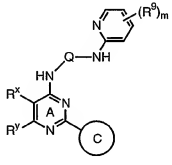
7. The compound of claim 1, wherein Q is -CH_2CH_2-, -$CH_2CH_2CH_2$-, or -$CH_2CH_2CH_2CH_2$-, -SO_2CH_2-, -CH_2SO_2-, -(C=O)CH_2-, or –CH_2(C=O)-.

8. The compound of claim 1, wherein B groups are selected from optionally substituted pyridyl, pyrimidinyl, thiazolyl, indolyl, imidazolyl, oxadiazolyl, tetrazolyl, pyrazinyl, triazolyl, thienyl, furanyl, quinolinyl, purinyl, naphthyl, benzothiazolyl, benzopyridyl,

benzimidazolyl, indazolyl, isothiazolyl, pyrazolyl, pyridazinyl, isoxazolyl, phenyl, benzothiophenyl, or pyridothiophenyl.

9. The compound of claim 8, wherein substituents for B groups are each independently selected from nitro, amino, cyano, halo, thioamido, amidino, oxamidino, alkoxyamidino, imidino, guanidino, sulfonamido, carboxyl, formyl, alkyl, haloalkyl, alkoxy, haloalkoxy, alkoxyalkyl, alkylaminoalkoxy, alkylcarbonyl, aralkylcarbonyl, heteroaralkylcarbonyl, alkylthio, aminoalkyl, cyanoalkyl, hydroxy, alkoxycarbonyl, aryl, aralkyl, heteroaryl, or heteroaralkyl.

10. The compound of claim 1, wherein B is optionally substituted 2-pyridyl and compounds have the general formula II:



II

wherein m is 0-4, and each occurrence of R^9 is independently selected from H, nitro, amino, cyano, halo, thioamido, amidino, oxamidino, alkoxyamidino, imidino, guanidino, sulfonamido, carboxyl, formyl, alkyl, haloalkyl, alkoxy, haloalkoxy, alkoxyalkyl, alkylaminoalkoxy, alkylcarbonyl, aralkylcarbonyl, heteroaralkylcarbonyl, alkylthio, aryl, aralkyl, heteroaryl, or heteroaralkyl.

11. The compound of claim 10, wherein R^9 substituents are selected from hydrogen, C_{1-4}alkyl, nitro, amino, cyano, cyanomethyl, trifluoromethyl, hydroxy, or methoxy.

12. The compound of claim 1, wherein B is indazolyl, pyrazolyl, or thiazolyl optionally substituted with one or more independent occurrences of R^9, wherein R^9 substituents are

selected from hydrogen, C_{1-4}alkyl, nitro, amino, cyano, cyanomethyl, trifluoromethyl, hydroxy, or methoxy.

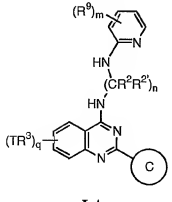
13. The compound of claim 1, wherein Ring C is optionally substituted phenyl or pyridinyl.

14. The compound of claim 1, wherein ring C is optionally substituted naphthyl, quinolinyl, isoquinolinyl or benzodioxolyl.

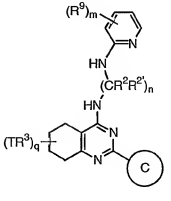
15. The compound of claim 13 or 14, wherein optional substituents on Ring C are selected from R^1 or R^5, wherein each occurrence of R^1 is independently selected from –halo, an optionally substituted C_{1-6} aliphatic group, phenyl, $-COR^6$, $-OR^6$, -CN, $-SO_2R^6$, $-SO_2NH_2$, $-N(R^6)_2$, $-CO_2R^6$, $-CONH_2$, $-NHCOR^6$, $-OC(O)NH_2$, or $-NHSO_2R^6$; and each occurrence of R^5 is selected from -halo, -CN, $-NO_2$, $-N(R^4)_2$, optionally substituted C_{1-6} aliphatic group, -OR', -C(O)R', $-CO_2R'$, $-CONH(R^4)$, $-N(R^4)COR'$, $-SO_2N(R^4)_2$, or $-N(R^4)SO_2R'$.

16. The compound of claim 15, wherein R^1 groups are selected from $-CF_3$, -Cl, -F, -CN, $-COCH_3$, $-OCH_3$, -OH, $-CH_2CH_3$, $-OCH_2CH_3$, $-CH_3$, $-CF_2CH_3$, cyclohexyl, t-butyl, isopropyl, cyclopropyl, -C≡CH, $-C\equiv C-CH_3$, $-SO_2CH_3$, $-SO_2NH_2$, $-N(CH_3)_2$, $-CO_2CH_3$, $-CONH_2$, $-NHCOCH_3$, $-OC(O)NH_2$, $-NHSO_2CH_3$, or $-OCF_3$; and R^5 groups are selected from -Cl, -F, -CN, $-CF_3$, $-NH_2$, $-NH(C_{1-4}$ aliphatic), $-N(C_{1-4}$ aliphatic$)_2$, $-O(C_{1-4}$ aliphatic), C_{1-4} aliphatic, or $-CO_2(C_{1-4}$ aliphatic).

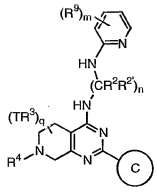
17. The compound of claim 1, having one of the formulas:



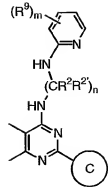
I-A-a



I-B-a



I-D-a



I-H-a

wherein q is 0-4, and T-R^3 substituents are selected from –R', halo, -OR', -C(=O)R', $-CO_2R'$, -COCOR', $-NO_2$, -CN, -S(O)R', $-SO_2R'$, -SR', $-N(R^4)_2$, $-CON(R^4)_2$, $-SO_2N(R^4)_2$, $-OC(=O)R'$, $-N(R^4)COR'$, $-N(R^4)CO_2$(optionally substituted C_{1-6} aliphatic), $-N(R^4)N(R^4)_2$, $-C=NN(R^4)_2$, -C=N-OR', $-N(R^4)CON(R^4)_2$, $-N(R^4)SO_2N(R^4)_2$, $-N(R^4)SO_2R'$, or $-OC(=O)N(R^4)_2$; and wherein m is 0-4, and each occurrence of R^9 is independently selected from H, nitro, amino, cyano, halo, thioamido, amidino, oxamidino, alkoxyamidino, imidino, guanidino, sulfonamido, carboxyl, formyl, alkyl, haloalkyl, alkoxy, haloalkoxy, alkoxyalkyl, alkylaminoalkoxy, alkylcarbonyl, aralkylcarbonyl, heteroaralkylcarbonyl, alkylthio, aryl, aralkyl, heteroaryl, or heteroaralkyl.

18. The compound of claim 17, wherein ring C is a phenyl ring and R^1 is halo, methyl, cyano, OMe, OH, or trifluoromethyl.

19. The compound of claim 1, wherein one or more of, or each of, B, ring C, R^X, R^Y, or R^1 is defined such that:

(a) B is an optionally substituted 5-6 membered monocyclic or 8-10 membered bicyclic aromatic ring, wherein said monocyclic or bicyclic ring has 1-4 heteroatoms selected from oxygen, sulfur or nitrogen;

(b) Ring C is a phenyl or pyridinyl ring having one or two ortho substituents independently selected from $–R^1$, wherein Ring C is further substituted by $–R^5$ and wherein when Ring C and two adjacent substituents thereon form a bicyclic ring system, the bicyclic ring system is selected from a naphthyl, quinolinyl or isoquinolinyl ring;

(c) R^X is hydrogen or C_{1-4} aliphatic and R^Y is T-R^3, or R^X and R^Y are taken together with their intervening atoms to form an optionally substituted 5-7 membered partially saturated or aromatic ring having 0-2 ring nitrogens; and

(d) R^1 is –halo, an optionally substituted C_{1-6} aliphatic group, phenyl, -COR^6, -OR^6, -CN, -SO_2R^6, -SO_2NH_2, -$N(R^6)_2$, -CO_2R^6, -$CONH_2$, -$NHCOR^6$, -$OC(O)NH_2$, or -$NHSO_2R^6$.

20. The compound of claim 1, wherein one or more of, or each of, B, R^2, ring C, R^X, R^Y, R^1, or R^5 is defined such that:

(a) B is an optionally substituted group selected from pyridyl, pyrimidinyl, thiazolyl, indolyl, imidazolyl, oxadiazolyl, tetrazolyl, pyrazinyl, triazolyl, thienyl, furanyl, quinolinyl, purinyl, naphthyl, benzothiazolyl, benzopyridyl, benzimidazolyl, indazolyl, isothiazolyl, pyrazolyl, pyridazinyl, isoxazolyl, phenyl, benzothiophenyl, or pyridothiophenyl;

(b) R^2 is H, alkyl, haloalkyl, heterocycloaminoalkyl, alkylaminoalkyl, and alkyl, wherein all alkyl moieties have 1-10 carbon atoms are unsubstituted;

(c) Ring C is a phenyl or pyridinyl ring having one or two ortho substituents independently selected from $–R^1$, wherein Ring C is further substituted by $–R^5$ and wherein when Ring C and two adjacent substituents thereon form a bicyclic ring system, the bicyclic ring system is a naphthyl ring;

(d) R^X is hydrogen or methyl and R^Y is –R', $N(R^4)_2$, or –OR', or R^X and R^Y are taken together with their intervening atoms to form a 5-7 membered partially saturated or aromatic carbocyclo ring optionally substituted with –R', halo, -OR', -C(=O)R', -CO_2R', -COCOR', -NO_2, -CN, -S(O)R', -SO_2R', -SR', -$N(R^4)_2$, -$CON(R^4)_2$, -$SO_2N(R^4)_2$, -OC(=O)R', -$N(R^4)$COR', -$N(R^4)CO_2$(optionally substituted C_{1-6} aliphatic), -$N(R^4)N(R^4)_2$, -C=NN$(R^4)_2$, -C=N-OR', -$N(R^4)CON(R^4)_2$, -$N(R^4)SO_2N(R^4)_2$, -$N(R^4)SO_2$R', or -$OC(=O)N(R^4)_2$;

(e) R^1 is –halo, a C_{1-6} haloaliphatic group, a C_{1-6} aliphatic group, phenyl, OMe, OH, or -CN; and

(f) each R^5 is independently selected from -halo, -CN, -NO_2, -$N(R^4)_2$, optionally substituted C_{1-6} aliphatic group, -OR', -C(O)R', -CO_2R', -$CONH(R^4)$, -$N(R^4)$COR', -$SO_2N(R^4)_2$, or -$N(R^4)SO_2$R'.

21. The compound of claim 1, wherein one or more of, or each of, B, R^2, ring C, R^X, R^Y, R^1, or R^5 is defined such that:

(a) B is an optionally substituted pyridyl group optionally substituted by 0, 1, or 2 occurrences of R^9, wherein each occurrence of R^9 is independently hydrogen, C_{1-4}alkyl, nitro, amino, cyano, cyanomethyl, trifluoromethyl, hydroxy, and methoxy;

(b) R^2 is H, alkyl, haloalkyl, heterocycloaminoalkyl, alkylaminoalkyl, and alkyl, wherein all alkyl moieties have 1-10 carbon atoms are unsubstituted;

(c) Ring C is a phenyl or pyridinyl ring having one or two ortho substituents independently selected from $-R^1$, wherein Ring C is further substituted by $-R^5$ and wherein when Ring C and two adjacent substituents thereon form a bicyclic ring system, the bicyclic ring system is a naphthyl ring;

(d) R^X is hydrogen or methyl and R^Y is –R', $N(R^4)_2$, or –OR', or R^X and R^Y are taken together with their intervening atoms to form a 5-7 membered partially saturated or aromatic ring having 1-2 nitrogen ring atoms optionally substituted with –R', halo, -OR', -C(=O)R', $-CO_2R'$, -COCOR', $-NO_2$, -CN, -S(O)R', $-SO_2R'$, -SR', $-N(R^4)_2$, $-CON(R^4)_2$, $-SO_2N(R^4)_2$, $-OC(=O)R'$, $-N(R^4)COR'$, $-N(R^4)CO_2$(optionally substituted C_{1-6} aliphatic), $-N(R^4)N(R^4)_2$, $-C=NN(R^4)_2$, $-C=N-OR'$, $-N(R^4)CON(R^4)_2$, $-N(R^4)SO_2N(R^4)_2$, $-N(R^4)SO_2R'$, or $-OC(=O)N(R^4)_2$;

(e) R^1 is –halo, a C_{1-6} haloaliphatic group, a C_{1-6} aliphatic group, phenyl, OMe, OH, or -CN; and

(f) each R^5 is independently selected from -halo, -CN, $-NO_2$, $-N(R^4)_2$, optionally substituted C_{1-6} aliphatic group, -OR', -C(O)R', $-CO_2R'$, $-CONH(R^4)$, $-N(R^4)COR'$, $-SO_2N(R^4)_2$, or $-N(R^4)SO_2R'$.

22. The compound of claim 1, wherein one or more of, or each of, B, R^2, ring C, R^X, R^Y, R^1, or R^5 is defined such that:

(a) B is an optionally substituted pyridyl group optionally substituted with 2 independent occurrences of R^9, wherein each occurrence of R^9 is independently hydrogen, C_{1-4}alkyl, nitro, amino, cyano, cyanomethyl, trifluoromethyl, hydroxy, and methoxy;

(b) each R^2 and $R^{2'}$ is H;

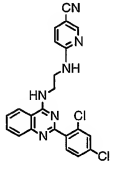
(c) Ring C is a phenyl ring having one or two ortho substituents independently selected from $-R^1$, wherein Ring C is further substituted by $-R^5$;

(d) R^X is hydrogen or methyl and R^Y is methyl, methoxymethyl, ethyl, cyclopropyl, isopropyl, t-butyl, alkyl- or an optionally substituted group selected from 2-pyridyl, 4-pyridyl, piperidinyl, or phenyl, or R^X and R^Y are taken together with their intervening atoms to form an optionally substituted benzo ring or partially saturated 6-membered carbocyclo ring;

(e) R^1 is –halo, a C_{1-4} aliphatic group optionally substituted with halogen, OMe, OH, or -CN; and

(f) each R^5 is independently selected from -Cl, -F, -CN, $-CF_3$, $-NH_2$, $-NH(C_{1-4}$ aliphatic), $-N(C_{1-4}$ aliphatic$)_2$, $-O(C_{1-4}$ aliphatic), optionally substituted C_{1-4} aliphatic, and $-CO_2(C_{1-4}$ aliphatic).

23. The compound of claim 1, selected from one of the compounds:



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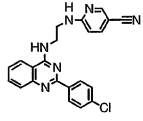

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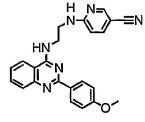

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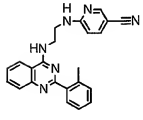

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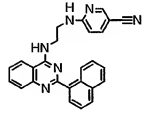

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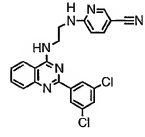

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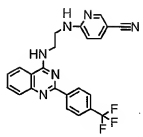

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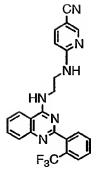

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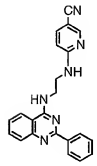

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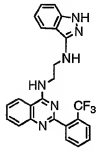

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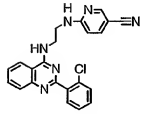

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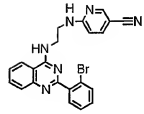

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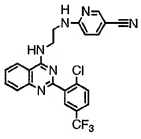

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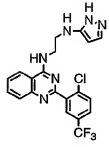

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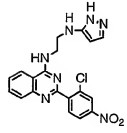

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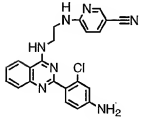

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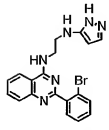

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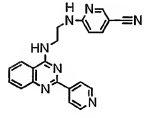

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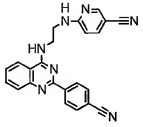

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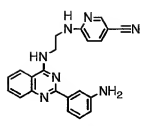

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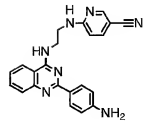

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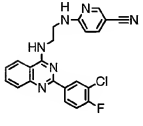

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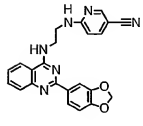

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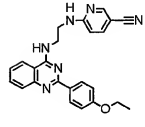

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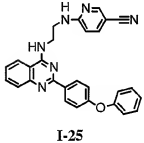

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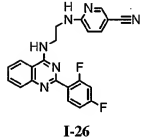

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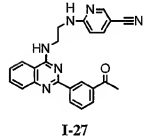

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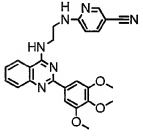

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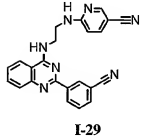

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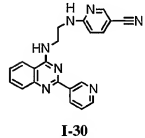

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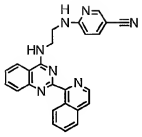

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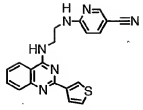

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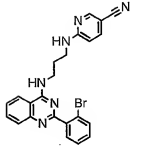

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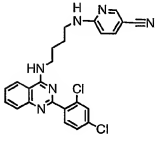

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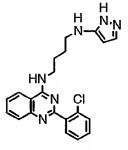

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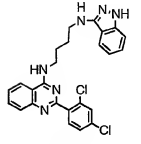

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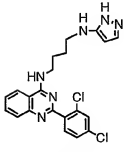

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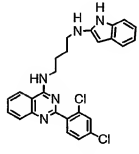

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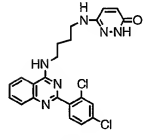

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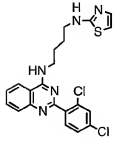

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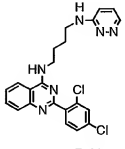

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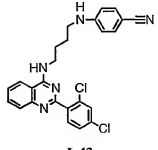

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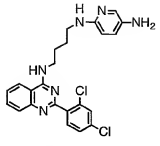

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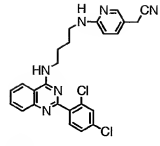

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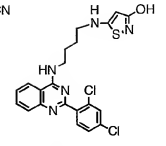

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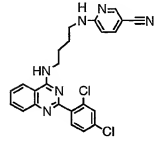

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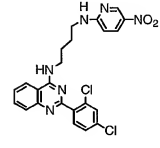

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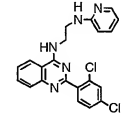

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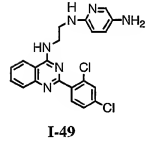

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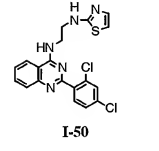

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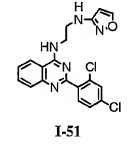

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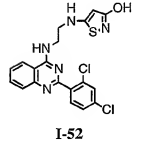

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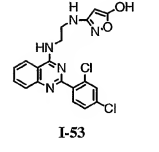

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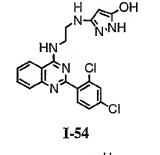

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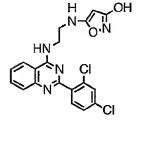

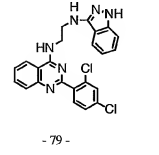

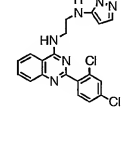

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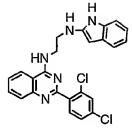

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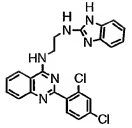

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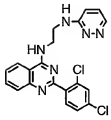

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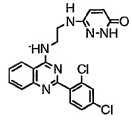

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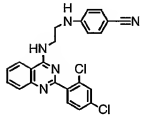

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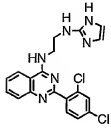

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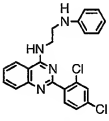

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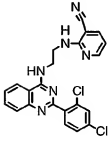

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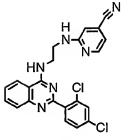

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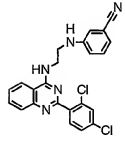

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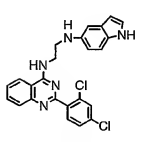

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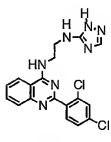

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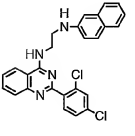

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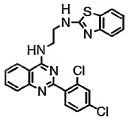

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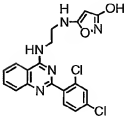

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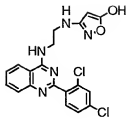

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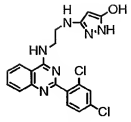

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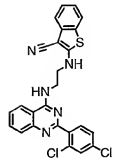

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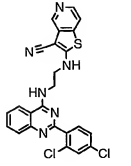

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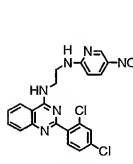

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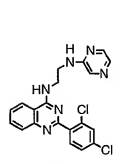

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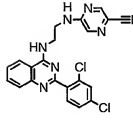
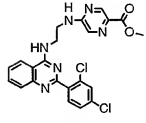


I-77

I-78

I-79

I-80



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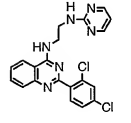

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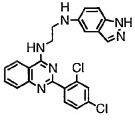

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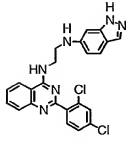

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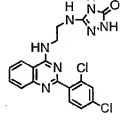

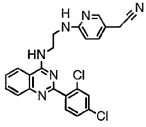

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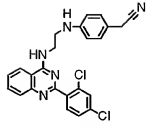

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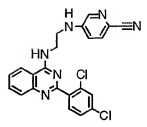

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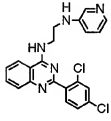

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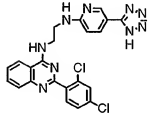

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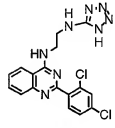

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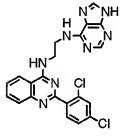

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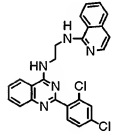

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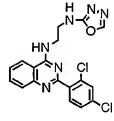

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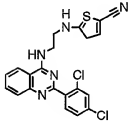

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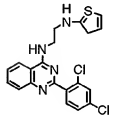

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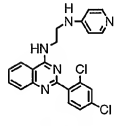

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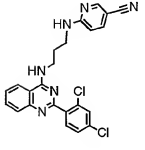

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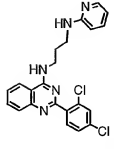

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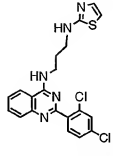
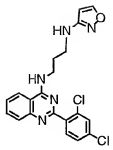
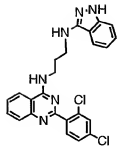


I-99



I-100



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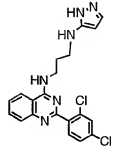

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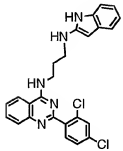

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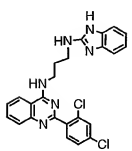

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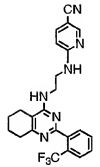

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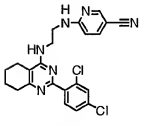

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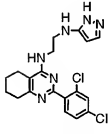

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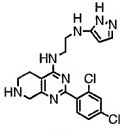

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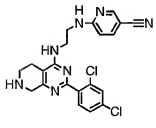
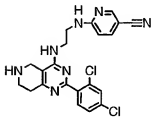


I-109



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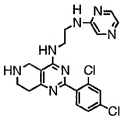

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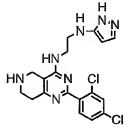

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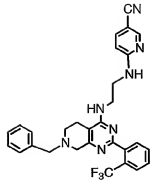

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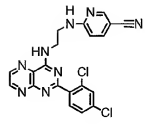

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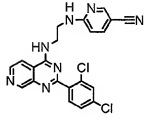

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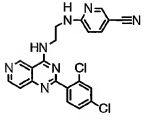

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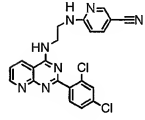

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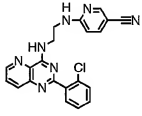

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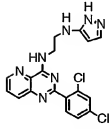

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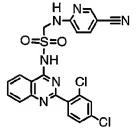

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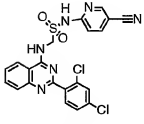

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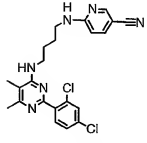

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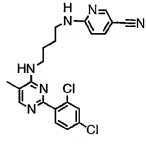

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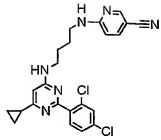

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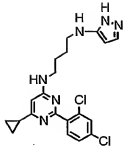

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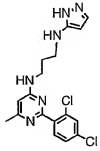

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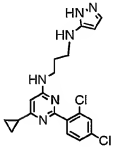

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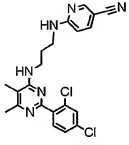

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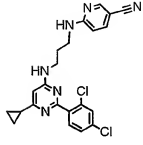

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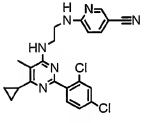

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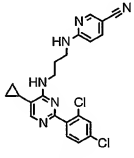

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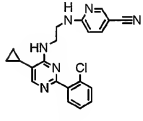

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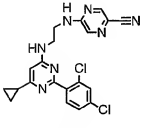

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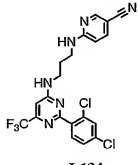

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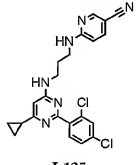

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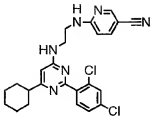

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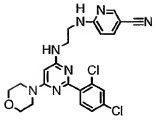

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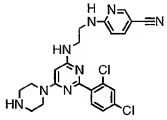
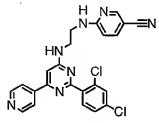


I-138



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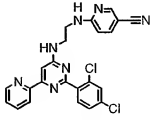

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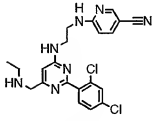

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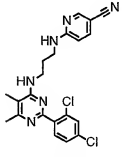

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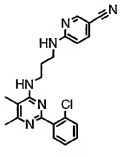

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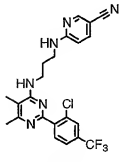

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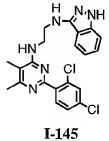
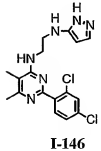


I-145



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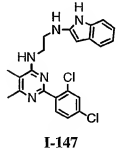

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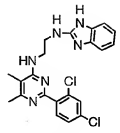
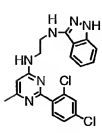
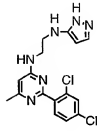


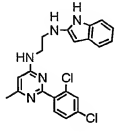
I-148



I-149



I-150



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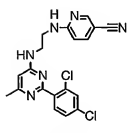

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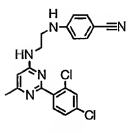
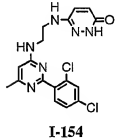
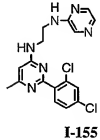


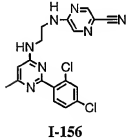
I-153



I-154



I-155



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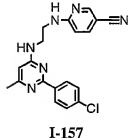

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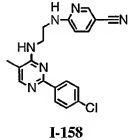

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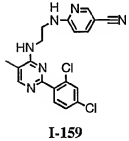

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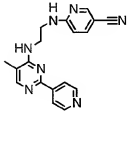

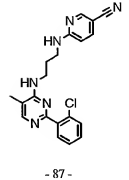

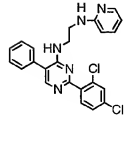

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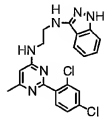

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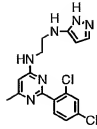

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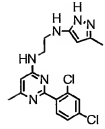

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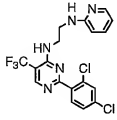

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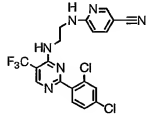

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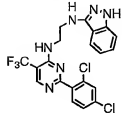

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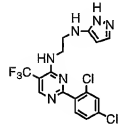

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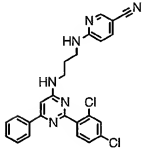

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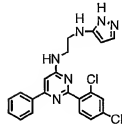

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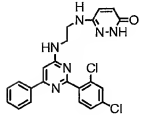

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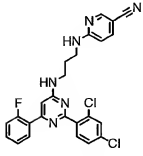

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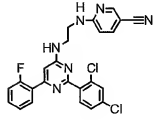

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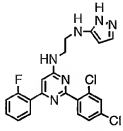

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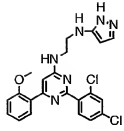

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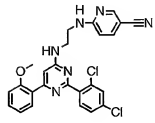

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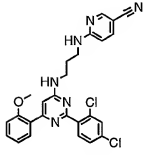

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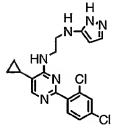

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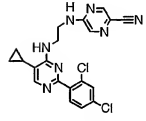

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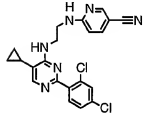

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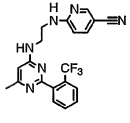

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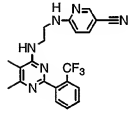

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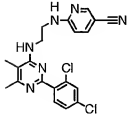

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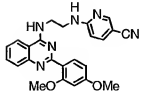

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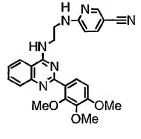

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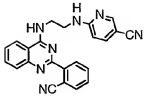

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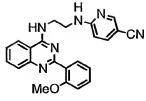

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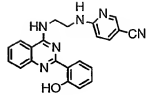

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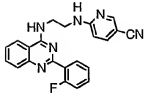

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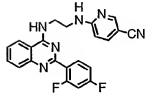

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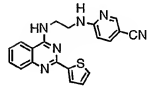

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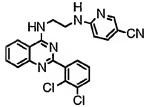

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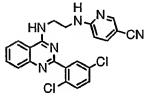

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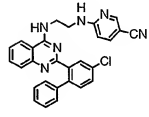

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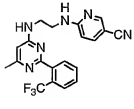

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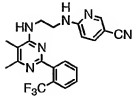

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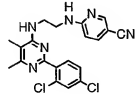

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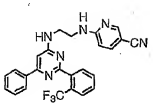

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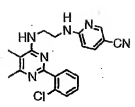

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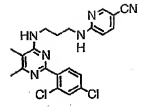

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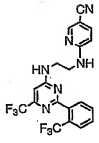

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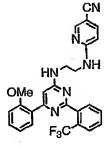

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24. A composition comprising a compound of claim 1, and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

25. A composition comprising a therapeutically effective amount of a compound of claim 1, and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

26. The composition of claim 25, wherein the therapeutically effective amount is an amount capable of inhibiting GSK-3 activity.

27. The composition of claim 24, further comprising one of more additional therapeutic agents.

28. A method of inhibiting GSK-3 kinase activity in a biological sample, comprising the step of contacting said biological sample with:

a) a composition according to claim 25; or

b) a compound according to claim 1.

29. A method of treating or lessening the severity of an autoimmune disease, an inflammatory disease, a metabolic disorder, a neurological or neurodegenerative disorder, or a cardiovascular disease in a patient, comprising the step of administering to said patient:

a) a composition according to claim 25; or

b) a compound according to claim 1.

30. The method of claim 29, wherein the disease is selected from allergy, asthma, diabetes, Alzheimer's disease, Huntington's disease, Parkinson's disease, AIDS-associated dementia, amyotrophic lateral sclerosis (AML, Lou Gehrig's disease), multiple sclerosis (MS), schizophrenia, cardiomyocyte hypertrophy, reperfusion/ischemia, stroke, or baldness.

31. The method of claim 29, wherein the disease is stroke.

32. The method of claim 29, wherein the disease is a neurological or neurodegenerative disorder.

33. The method of claim 29, comprising the additional step of administering to said patient an additional therapeutic agent selected from a treatment for Alzheimer's Disease, a treatment for Parkinson's Disease, an agent for treating Multiple Sclerosis (MS), a treatment for asthma, an anti-inflammatory agent, an immunomodulatory or immunosuppressive agent, a neurotrophic factor, an agent for treating stroke, an agent for treating cardiovascular disease, or an agent for treating diabetes, wherein:

said additional therapeutic agent is appropriate for the disease being treated; and

said additional therapeutic agent is administered together with said composition as a single dosage form or separately from said composition as part of a multiple dosage form.

34. A method of treating or lessening the severity of a GSK-3-mediated disease or condition in a patient, comprising the step of administering to said patient:

a) a composition according to claim 25; or

b) a compound according to claim 1.

35. The method of claim 34, wherein said GSK-3-mediated disease is selected from an autoimmune disease, an inflammatory disease, a metabolic disorder, a neurological or neurodegenerative disorder, or a cardiovascular disease.

36. The method of claim 34, wherein said GSK-3-mediated disease is selected from allergy, asthma, diabetes, Alzheimer's disease, Huntington's disease, Parkinson's disease, AIDS-associated dementia, amyotrophic lateral sclerosis (AML, Lou Gehrig's disease), multiple sclerosis (MS), schizophrenia, cardiomyocyte hypertrophy, reperfusion/ischemia, stroke, or baldness.

37. The method of claim 34, wherein said GSK-3-mediated disease is stroke.

38. The method of claim 34, wherein said GSK-3-mediated disease is a neurological or neurodegenerative disorder.

39. The method of claim 34, comprising the additional step of administering to said patient an additional therapeutic agent selected from a treatment for Alzheimer's Disease, a treatment for Parkinson's Disease, an agent for treating Multiple Sclerosis (MS), a treatment for asthma, an anti-inflammatory agent, an immunomodulatory or immunosuppressive agent, a neurotrophic factor, an agent for treating stroke, an agent for treating cardiovascular disease, or an agent for treating diabetes, wherein:

said additional therapeutic agent is appropriate for the disease being treated; and

said additional therapeutic agent is administered together with said composition as a single dosage form or separately from said composition as part of a multiple dosage form.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 02/39190

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/506 C07D239/94 A61P35/00 C07D401/12 C07D403/12
C07D405/14 C07D409/14 C07D417/12 C07D413/12 C07D409/12
C07D401/04 C07D409/04 C07D495/04 C07D471/04 C07D475/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data, WPI Data, BEILSTEIN Data, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 02 053557 A (WELLER THOMAS ;BOLLI MARTIN (CH); BOSS CHRISTOPH (CH); FISCHLI WAL) 11 July 2002 (2002-07-11) claims 1,14 page 49 -page 50 page 65 -page 72 page 108 -page 109 page 122 -page 123 page 185 -page 188 --- -/--	1-27, 29-39

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

'A' document defining the general state of the art which is not considered to be of particular relevance

'E' earlier document but published on or after the international filing date

'L' document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

'O' document referring to an oral disclosure, use, exhibition or other means

'P' document published prior to the international filing date but later than the priority date claimed

'T' later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

'X' document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

'Y' document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

'&' document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 February 2003	14/03/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Kollmannsberger, M

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 02/39190

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/519

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	DATABASE CHEMCATS 'Online! CHEMICAL ABSTRACTS SERVICES COLUMBUS, OHIO, US; XP002232960 order numbers: RDR03878; RDR03879; RDR03877; RDR03876; RDR03874; RDR03871; RDR03870; RH 02109 & "Maybridge HTS" 11 November 2002 (2002-11-11) , MAYBRIDGE PLC , TINAGEL, CORNWALL, PL34 0HW UNITED KINGDOM ---	1-27
P,Y	WO 02 22605 A (KNEGTEL RONALD ;BEBBINGTON DAVID (GB); CHARRIER JEAN DAMIEN (GB);) 21 March 2002 (2002-03-21) claims --- -/—	1-39

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

'A' document defining the general state of the art which is not considered to be of particular relevance

'E' earlier document but published on or after the international filing date

'L' document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

'O' document referring to an oral disclosure, use, exhibition or other means

'P' document published prior to the international filing date but later than the priority date claimed

'T' later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

'X' document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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'&' document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 February 2003	

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Kollmannsberger, M

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 02/39190

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 99 65897 A (RAMURTHY SAVITHRY ;CHIRON CORP (US); GOFF DANE (US); NUSS JOHN M () 23 December 1999 (1999-12-23) claims examples	1-39
Y	WO 01 44206 A (RAMURTHY SAVITHRI ;CHIRON CORP (US); NUSS JOHN M (US)) 21 June 2001 (2001-06-21) claims examples	1-39
Y	WO 01 44246 A (CHIRON CORP ;NUSS JOHN M (US); ZHOU XIAOHUI A (US)) 21 June 2001 (2001-06-21) claims examples	1-39
X	VAN MUIJLWIJK-KOEZEN ET AL: "Isoquinoline and Quinazoline Urea Analogues as Antagonists for the Human Adenosine A3 Receptor" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY, US, vol. 43, no. 5, 1 June 2000 (2000-06-01), pages 2227-2338, XP002147879 ISSN: 0022-2623 page 2227, column 1 page 2230 -page 2231; table 1	1-27, 29-39
X	EP 0 826 673 A (DAINIPPON PHARMACEUTICAL CO) 4 March 1998 (1998-03-04) claims 1,18-23 examples 63,204	1-27, 29-39
X	WO 98 09960 A (DAINIPPON PHARMACEUTICAL CO ;MURATA TERUYA (JP); KONDO KATSUNORI () 12 March 1998 (1998-03-12) claim 1 examples 13,47,49 abstract	1-27, 29-39
X	US 3 506 665 A (SANTILLI ARTHUR A ET AL) 14 April 1970 (1970-04-14) claims 1,5,9	1-27

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 02/39190

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE CA 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; KOMKOV, A. V. ET AL: "5-Acetyl-6-amino-4-(methylthio)-2-phenylpyrimidine and its use in the synthesis of functionalized pyrido'2,3-d!pyrimidines and pyrimido'4,5-d!pyrimidines" retrieved from STN Database accession no. 124:117226 XP002232961 abstract & IZVESTIYA AKADEMII NAUK, SERIYA KHIMICHESKAYA (1995), (7), 1324-8 , -----	1-27

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 02/39190

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 28-39 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: 1-39 (in part)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-39 (in part)

The claims are partly directed to "pharmaceutically acceptable derivatives or prodrugs" of structurally defined compounds. Since there is no further explanation in the description which derivatives (in terms of structural features) are meant to be covered by such a definition, unclarity (Art. 6 PCT) arises to such an extent as to make a meaningful search impossible. The search has been restricted to compounds structurally defined in the claims.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US 02/39190

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 02053557 A	11-07-2002	WO 02053557 A1	11-07-2002
WO 0222605 A	21-03-2002	AU 9091201 A	26-03-2002
		AU 9091401 A	26-03-2002
		AU 9094401 A	26-03-2002
		AU 9101301 A	26-03-2002
		AU 9267001 A	26-03-2002
		AU 9455801 A	26-03-2002
		AU 9687101 A	26-03-2002
		AU 9687501 A	26-03-2002
		WO 0222603 A1	21-03-2002
		WO 0222601 A1	21-03-2002
		WO 0222604 A1	21-03-2002
		WO 0222605 A1	21-03-2002
		WO 0222606 A1	21-03-2002
		WO 0222607 A1	21-03-2002
		WO 0222608 A1	21-03-2002
		WO 0222602 A2	21-03-2002
		AU 3116602 A	01-07-2002
		AU 3404702 A	01-07-2002
		WO 02066461 A1	29-08-2002
		WO 0250065 A2	27-06-2002
		WO 02057259 A2	25-07-2002
		WO 0250066 A2	27-06-2002
		WO 02059112 A2	01-08-2002
		WO 02068415 A1	06-09-2002
		WO 02062789 A1	15-08-2002
		WO 02059111 A2	01-08-2002
		US 2003004161 A1	02-01-2003
		US 2003022885 A1	30-01-2003
		US 2003004164 A1	02-01-2003
WO 9965897 A	23-12-1999	AU 4956699 A	05-01-2000
		CN 1312807 T	12-09-2001
		EP 1087963 A1	04-04-2001
		WO 9965897 A1	23-12-1999
		US 6417185 B1	09-07-2002
		US 6489344 B1	03-12-2002
WO 0144206 A	21-06-2001	AU 2436701 A	25-06-2001
		EP 1237880 A2	11-09-2002
		WO 0144206 A1	21-06-2001
		US 2001034051 A1	25-10-2001
WO 0144246 A	21-06-2001	AU 2580201 A	25-06-2001
		EP 1240168 A1	18-09-2002
		WO 0144246 A1	21-06-2001
		US 2003008866 A1	09-01-2003
		US 2001044436 A1	22-11-2001
EP 0826673 A	04-03-1998	AT 228113 T	15-12-2002
		AU 694647 B2	23-07-1998
		AU 5287496 A	30-10-1996
		BR 9604894 A	14-07-1998
		DE 69624916 D1	02-01-2003
		EP 0826673 A1	04-03-1998
		NO 974685 A	12-12-1997
		NZ 304982 A	29-03-1999

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US 02/39190

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0826673 A		PL 322819 A1	16-02-1998
		RO 117532 B1	30-04-2002
		SK 137497 A3	06-05-1998
		US 5972946 A	26-10-1999
		CA 2218033 A1	17-10-1996
		CN 1186487 A ,B	01-07-1998
		CZ 9703223 A3	18-02-1998
		HU 9801688 A2	29-03-1999
		IL 117659 A	06-12-2000
		WO 9632383 A1	17-10-1996
		RU 2160256 C2	10-12-2000
		TW 450963 B	21-08-2001
		ZA 9602438 A	01-10-1996
WO 9809960 A	12-03-1998	AU 4134297 A	26-03-1998
		WO 9809960 A1	12-03-1998
US 3506665 A	14-04-1970	NONE	